```
GGCAT   IS MCY  UNS  AT  27
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E6 C  AT  27

GRAPH ATTRIBUTES:
RSPEC   3  22
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74

100.0% PROCESSED    2731 ITERATIONS                          1228 ANSWERS
SEARCH TIME: 00.00.01


=> d que nos l108
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108       1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76


=> d que nos l84
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17             QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY
                <2003 OR REVIEW/DT
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20           - QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L21             QUE  ABB=ON  PLU=ON  CANCER+PFT,OLD,NEW,NT/CT
L22             QUE  ABB=ON  PLU=ON  "CANCER (SYNDROME)"+PFT,OLD,NEW,NT/C
                T
```

```
L23             QUE  ABB=ON   PLU=ON   NEOPLASM+PFT,OLD,NEW,NT/CT
L24             QUE  ABB=ON   PLU=ON   "ANTITUMOR AGENTS"+PFT,OLD,NEW,NT/CT
L25             QUE  ABB=ON   PLU=ON   A61P0035/IPC OR A61P0035-00/IPC OR A
                61P0035-02/IPC OR A61P0035-04/IPC
L26          28 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L13
L27      345902 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L3
L28        4251 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L26 OR L27) (L) (L19 OR L20)

L29        3790 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L28 AND (L21 OR L22 OR L23 OR
                L24 OR L25)
L30        7141 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L26 OR L27) (L) (THU OR PKT
                OR PAC OR DMA OR BAC)/RL
L31         268 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L29 AND L30
L32           4 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L31 AND (L14 OR L15 OR L16)
L39         870 SEA FILE=REGISTRY ABB=ON   PLU=ON   L7 AND NCSC2/ES
L40         328 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L39
L43         304 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L26 OR L27) (L)((L19 OR
                L20)(L)(THU OR PKT OR PAC OR DMA OR BAC)/RL)
L45         266 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L43 AND (L21 OR L22 OR L23 OR
                L24 OR L25)
L46           5 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L45 AND L26
L47           2 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L46 AND L40
L48         262 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L45 NOT L32
L49         150 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L48 AND L17
L50           1 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L46
L51           0 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L47
L52           8 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L26 OR L40)(L)(L19 OR L20)
L53           2 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L52
L54          23 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L26 OR L40) AND (L21 OR L22
                OR L23 OR L24 OR L25)
L55           2 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L54
L56         133 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L24
L57          57 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L8
L58           1 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L49 AND L57
L59             TRANSFER  PLU=ON  L56 1- RN :    6672 TERMS
L60        6672 SEA FILE=REGISTRY ABB=ON   PLU=ON   L59
L61           2 SEA FILE=REGISTRY ABB=ON   PLU=ON   L7 AND L60
L62           2 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L56 AND L61
L63           2 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L50 OR L51) OR L53 OR L55 OR
                L58 OR L62
L64          18 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L57 AND (L19 OR L20 OR L21 OR
                L22 OR L23 OR L24 OR L25)
L65          19 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L63 OR L64
L66          14 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L65 AND (L14 OR L15 OR L16)
L67          14 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L66 OR L32
L68           5 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L65 NOT L67
L69           3 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L68 AND L17
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L77          11 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L76 (L)(L19 OR L20)
L78          29 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L76 AND (L21 OR L22 OR L23 OR
                L24 OR L25)
L79          30 SEA FILE=HCAPLUS ABB=ON   PLU=ON   (L77 OR L78)
L80          10 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L79 AND (L14 OR L15 OR L16)
L81          20 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L79 NOT L80
L82          10 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L81 AND L17
L84          10 SEA FILE=HCAPLUS ABB=ON   PLU=ON   L82 OR L50 OR L51 OR L53 OR
                L55 OR L58 OR L69
```

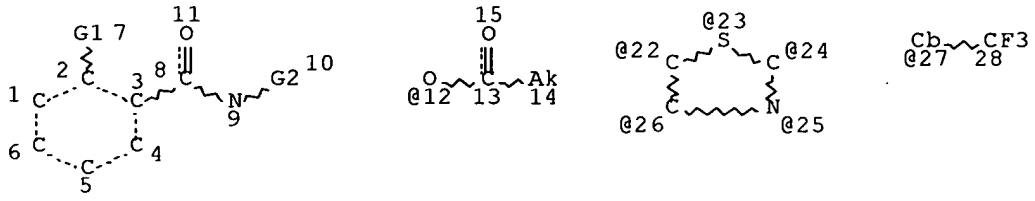
```
=> d his l92

     (FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 12:26:46 ON 30 NOV 2007)
L92            0 S L90 NOT L91

=> d que nos l92
L5               STR
L7          2808 SEA FILE=REGISTRY SSS FUL L5
L14              QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15              QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16              QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19              QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                 OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                 MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                 N?
L20              QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                 OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                 LYMPHOM?
L25              QUE  ABB=ON  PLU=ON  A61P0035/IPC OR A61P0035-00/IPC OR A
                 61P0035-02/IPC OR A61P0035-04/IPC
L74              STR
L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L86          549 SEA FILE=REGISTRY ABB=ON  PLU=ON  L76 AND (USPATFULL OR USPAT2
                 OR USPATOLD)/LC
L87          126 SEA L86
L88            2 SEA L87 AND L25
L89            2 SEA L88 AND (L19/IT,TI,CC,CT,ST,STP OR L20/IT,TI,CC,CT,ST,STP)

L90            2 SEA (L88 OR L89)
L91           13 SEA L87 AND (L14 OR L15 OR L16)
L92            0 SEA L90 NOT L91


=> d que stat l97
L74              STR
```




```
VAR G1=OH/12
VAR G2=22/23/24/25/26/27
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   9
CONNECT IS E1  RC AT  14
CONNECT IS E3  RC AT  27
DEFAULT MLEVEL IS ATOM
GGCAT   IS MCY  UNS  AT  27
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E6 C  AT  27

GRAPH ATTRIBUTES:
RSPEC   3  22
```

```
NUMBER OF NODES IS  22

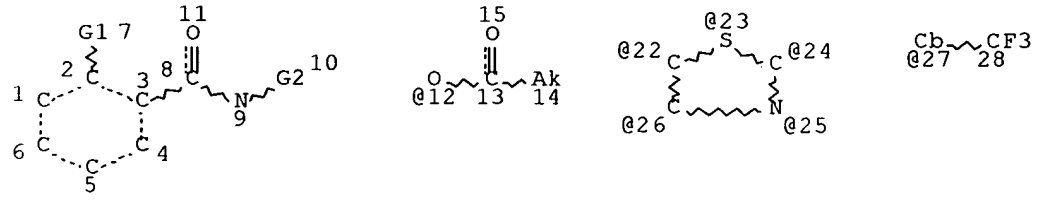
STEREO ATTRIBUTES: NONE
L97         104 SEA FILE=WPIX SSS FUL L74

100.0% PROCESSED    1589 ITERATIONS                          104 ANSWERS
SEARCH TIME: 00.00.05


=> d his l97-l107

     (FILE 'WPIX' ENTERED AT 12:29:38 ON 30 NOV 2007)
L97         104 S L74 FUL
                SAVE TEMP L97 RAE292WPIS/A
L98          32 S L97/DCR
                SELECT L97 1- SDCN
L99          32 S E72-E175/DCN
L100         32 S L98-L99
L101         10 S L100 AND (L95 OR L25 OR (P633 OR P631 OR P632)/M0,M1,M2,M3,M
L102         10 S L100 AND L19-L20
L103         10 S L101 AND L102
L104         10 S L101-L103
L105          6 S L104 AND L14-L16
L106          4 S L104 NOT L105
L107          0 S L106 AND L18

=> d que l107
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L18             QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L25             QUE  ABB=ON  PLU=ON  A61P0035/IPC OR A61P0035-00/IPC OR A
                61P0035-02/IPC OR A61P0035-04/IPC
L74             STR
```




```
VAR G1=OH/12
VAR G2=22/23/24/25/26/27
NODE ATTRIBUTES:
CONNECT IS E2  RC AT   9
CONNECT IS E1  RC AT  14
CONNECT IS E3  RC AT  27
```

```
DEFAULT MLEVEL IS ATOM
GGCAT   IS MCY  UNS  AT  27
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E6 C  AT  27

GRAPH ATTRIBUTES:
RSPEC   3  22
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L95             QUE  ABB=ON  PLU=ON  (B14-H01 OR C14-H01 OR B14-H01? OR C
                14-H01?)/MC
L97         104 SEA FILE=WPIX SSS FUL L74
L98          32 SEA FILE=WPIX ABB=ON  PLU=ON  L97/DCR
L99          32 SEA FILE=WPIX ABB=ON  PLU=ON  (RAAFWU/DCN OR RACQNZ/DCN OR
                RACQX0/DCN OR RACRDB/DCN OR RACRDC/DCN OR RACRDD/DCN OR
                RACRDE/DCN OR RACRDF/DCN OR RACRDG/DCN OR RACRDH/DCN OR
                RACRDI/DCN OR RACRDJ/DCN OR RACRDK/DCN OR RACRDL/DCN OR
                RACRDM/DCN OR RACRDN/DCN OR RACRDO/DCN OR RACRDP/DCN OR
                RACRDQ/DCN OR RACRDR/DCN OR RACRDS/DCN OR RACRDT/DCN OR
                RACRDV/DCN OR RACRDX/DCN OR RACRDY/DCN OR RACRDZ/DCN OR
                RACRE0/DCN OR RACRE1/DCN OR RACRE2/DCN OR RACRRD/DCN OR
                RACRRE/DCN OR RACRRF/DCN OR RACVTE/DCN OR RACVTF/DCN OR
                RACVTK/DCN OR RACVTM/DCN OR RACVTN/DCN OR RACVTO/DCN OR
                RACVTP/DCN OR RACVTQ/DCN OR RACVTT/DCN OR RACVTU/DCN OR
                RACVTV/DCN OR RACVTW/DCN OR RACVTX/DCN OR RACVTY/DCN OR
                RACVTZ/DCN OR RACVU0/DCN OR RACVU1/DCN OR RACVU2/DCN OR
                RACVU3/DCN OR RACVU4/DCN OR RACWGE/DCN OR RACWGF/DCN OR
                RAC72I/DCN OR RAGUJA/DCN OR RAGUJB/DCN OR RAGUJC/DCN OR
                RAGUJD/DCN OR RAGUJE/DCN OR RAGUJF/DCN OR RAGUJG/DCN OR
                RAGUJH/DCN OR RAGUJI/DCN OR RAGUJJ/DCN OR RAGUJK/DCN OR
                RAGUJL/DCN OR RAGUJM/DCN OR RAGUJN/DCN OR RAGUJO/DCN OR
                RAHG3A/DCN OR RAIX7Z/DCN OR RAMFVC/DCN OR RAM4LO/DCN OR
                RAM4LP/DCN OR RAM4LQ/DCN OR RAM4LR/DCN OR RAM4LS/DCN OR
                RAM4LT/DCN OR RANL8F/DCN OR RANL8G/DCN OR RANL8H/DCN OR
                RANL8I/DCN OR RANL8R/DCN OR RANL8S/DCN OR RANL8T/DCN OR
                RANL8U/DCN OR RAN3RR/DCN OR RAN3RU/DCN OR RAN3RV/DCN OR
                RAOIRH/DCN OR RAOIRI/DCN OR RAOIRJ/DCN OR RAOIRL/DCN OR
                RAOIRM/DCN OR RAPE56/DCN OR RA0F6S/DCN OR RA0F6T/DCN OR
                RA0F6U/DCN OR RA0F71/DCN OR RA0F72/DCN OR RA0F73/DCN OR
                RA5NA8/DCN OR RA75IT/DCN)
L100         32 SEA FILE=WPIX ABB=ON  PLU=ON  (L98 OR L99)
L101         10 SEA FILE=WPIX ABB=ON  PLU=ON  L100 AND (L95 OR L25 OR (P633 OR
                P631 OR P632)/M0,M1,M2,M3,M4,M5,M6)
L102         10 SEA FILE=WPIX ABB=ON  PLU=ON  L100 AND (L19 OR L20)
L103         10 SEA FILE=WPIX ABB=ON  PLU=ON  L101 AND L102
L104         10 SEA FILE=WPIX ABB=ON  PLU=ON  (L101 OR L102 OR L103)
L105          6 SEA FILE=WPIX ABB=ON  PLU=ON  L104 AND (L14 OR L15 OR L16)
L106          4 SEA FILE=WPIX ABB=ON  PLU=ON  L104 NOT L105
L107          0 SEA FILE=WPIX ABB=ON  PLU=ON  L106 AND L18


=> d que nos l115
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
```

```
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17             QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY
                <2003 OR REVIEW/DT
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108       1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L109          1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND MEDLINE/LC
L110        124 SEA FILE=MEDLINE ABB=ON  PLU=ON  L109
L111            QUE  ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENTS"+PFT,OLD,NEW,
                NT/CT
L112         22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L110 AND (L111 OR (L19 OR
                L20))
L113          0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L112 AND (L14 OR L15 OR L16)
L114         22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L112 NOT L113
L115         11 SEA FILE=MEDLINE ABB=ON  PLU=ON  L114 AND L17


=> d que nos l140
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17             QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY
                <2003 OR REVIEW/DT
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108       1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L116          6 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND EMBASE/LC
L117        337 SEA FILE=EMBASE ABB=ON  PLU=ON  L116
L118            QUE  ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+PFT,OLD,NEW,N
```

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                T/CT
L119          77 SEA FILE=EMBASE ABB=ON  PLU=ON  L117 AND (L118 OR (L19 OR
                L20))
L120           0 SEA FILE=EMBASE ABB=ON  PLU=ON  L119 AND (L14 OR L15 OR L16)
L121          77 SEA FILE=EMBASE ABB=ON  PLU=ON  L119 NOT L120
L122          55 SEA FILE=EMBASE ABB=ON  PLU=ON  L121 AND L17
L123             QUE  ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+PFT,OLD,NEW/C
                T
L124             QUE  ABB=ON  PLU=ON  "CANCER INHIBITION"+PFT,OLD,NEW,NT/C
                T
L125          25 SEA FILE=EMBASE ABB=ON  PLU=ON  L122 AND (L19 OR L20)
L126          44 SEA FILE=EMBASE ABB=ON  PLU=ON  L122 AND (L123 OR L124)
L127          55 SEA FILE=EMBASE ABB=ON  PLU=ON  (L125 OR L126)
L129         265 SEA FILE=EMBASE ABB=ON  PLU=ON  NITAZOXANIDE+PFT,OLD,NEW,NT/CT
                (L) DT/CT
L130          45 SEA FILE=EMBASE ABB=ON  PLU=ON  L127 AND L129
L131             QUE  ABB=ON  PLU=ON  NEOPLASM+PFT,OLD,NEW,NT/CT
L132             QUE  ABB=ON  PLU=ON  TUMOR+PFT,OLD,NEW,NT/CT
L133      240317 SEA FILE=EMBASE ABB=ON  PLU=ON  (L131 OR L132) (L) DT/CT
L134           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L127 AND L133
L135           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L134 NOT L120
L136           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L135 AND L17
L137           5 SEA FILE=EMBASE ABB=ON  PLU=ON  L130 AND L133
L138           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L136 OR L137
L139           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L138 NOT L120
L140           6 SEA FILE=EMBASE ABB=ON  PLU=ON  L139 AND L17


=> d his l146

     (FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 12:50:14 ON 30
     NOV 2007)
L146           6 S L145 AND L17

=> d que nos l146
L1             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3               TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4           561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5               STR
L7          2808 SEA FILE=REGISTRY SSS FUL L5
L8           187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9            10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14              QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15              QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16              QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17              QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY
                <2003 OR REVIEW/DT
L19              QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20              QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L74              STR
L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
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L108       1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L141          4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND (BIOSIS OR CABA OR
                BIOTECHNO OR DRUGU OR VETU)/LC
L142        210 SEA L141
L143         12 SEA L142 AND (L19 OR L20)
L144          0 SEA L143 AND (L14 OR L15 OR L16)
L145         12 SEA L143 NOT L144
L146          6 SEA L145 AND L17


=> d his l159

     (FILE 'MEDLINE, BIOSIS, EMBASE, PASCAL, LIFESCI, BIOENG, CABA, AGRICOLA,
     BIOTECHNO, BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI,
     DISSABS' ENTERED AT 12:53:26 ON 30 NOV 2007)
L159          9 S L158 AND (L149 (10A) (TREAT? OR THERAP?))

     FILE 'STNGUIDE' ENTERED AT 13:17:45 ON 30 NOV 2007

=> d que nos l159
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17             QUE  ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY
                <2003 OR REVIEW/DT
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108       1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L109          1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND MEDLINE/LC
L116          6 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND EMBASE/LC
L141          4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND (BIOSIS OR CABA OR
                BIOTECHNO OR DRUGU OR VETU)/LC
L147          9 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L109 OR L116 OR L141
L148            SEL  PLU=ON  L147 1- NAME :      24 TERMS
L149       7188 SEA L148
L150       1006 SEA L149 AND (L19 OR L20)
L151         33 SEA L150 AND (L14 OR L15 OR L16)
L153        973 SEA L150 NOT L151
L154        723 SEA L153 AND (L19/IT,TI,CC,CT,ST,STP OR L20/IT,TI,CC,CT,ST,STP)

L155       1878 SEA L148/IT,TI,CC,CT,ST,STP
L156        153 SEA L154 AND L155
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L157          60 SEA L156 AND L17
L158          46 SEA L157 AND (CLINIC? OR THERAP? OR TREAT? OR MEDIC? OR
                 CHEMOTHERAP?)/IT,TI,CC,CT,ST,STP
L159           9 SEA L158 AND (L149 (10A) (TREAT? OR THERAP?))


=> dup rem l84 l92 l107 l115 l140 l146 l159
L92 HAS NO ANSWERS
L107 HAS NO ANSWERS
FILE 'HCAPLUS' ENTERED AT 13:20:50 ON 30 NOV 2007
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PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L92
PROCESSING COMPLETED FOR L107
PROCESSING COMPLETED FOR L115
PROCESSING COMPLETED FOR L140
PROCESSING COMPLETED FOR L146
PROCESSING COMPLETED FOR L159
L160          40 DUP REM L84 L92 L107 L115 L140 L146 L159 (2 DUPLICATES REMOVED)
                 ANSWERS '1-10' FROM FILE HCAPLUS
                 ANSWERS '11-21' FROM FILE MEDLINE
                 ANSWERS '22-28' FROM FILE EMBASE
                 ANSWERS '29-32' FROM FILE BIOSIS
                 ANSWER '33' FROM FILE BIOTECHNO
                 ANSWERS '34-39' FROM FILE DRUGU
                 ANSWER '40' FROM FILE SCISEARCH


=> file stnguide
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L*** DEL       0 S L8 AND (F/2 AND CL/1)

     FILE 'STNGUIDE' ENTERED AT 11:29:15 ON 30 NOV 2007

     FILE 'REGISTRY' ENTERED AT 11:29:47 ON 30 NOV 2007
L9            10 SEA ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
                 D SCAN
L10            0 SEA ABB=ON  PLU=ON  L9 AND "BENZAMIDE, N-[3,5-BIS(TRIFLUOROMETH
                 YL)PHENYL]-5-CHLORO-2-HYDROXY-"/CN
L11            0 SEA ABB=ON  PLU=ON  L9 AND "BENZAMIDE, N-[3,5-BIS(TRIFLUOROMETH
                 YL)PHENYL]-5-CHLORO-2-HYDROXY-"/IN
L12            3 SEA ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETHYL)PHENYL"/CNS
                  AND "5-CHLORO-2-HYDROXY"/CNS
                 D SCAN
L13            1 SEA ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N O2"/MF
                 D SCAN

     FILE 'STNGUIDE' ENTERED AT 11:34:04 ON 30 NOV 2007
                 D QUE STAT

     FILE 'REGISTRY' ENTERED AT 11:34:22 ON 30 NOV 2007
                 D IDE L13

     FILE 'STNGUIDE' ENTERED AT 11:34:23 ON 30 NOV 2007

     FILE 'ZCAPLUS' ENTERED AT 11:35:17 ON 30 NOV 2007
L14              QUE ABB=ON  PLU=ON  MUTO, S?/AU
L15              QUE ABB=ON  PLU=ON  ITAI, A?/AU
L16              QUE ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L17              QUE ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003
                 OR REVIEW/DT
L18              QUE ABB=ON  PLU=ON  AY<2003 OR PY<2003 OR PRY<2003
L19              QUE ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NEOPLAS?
                 OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?MELANOM? OR
                 ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKIN?
L20              QUE ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINEOPLAS?
                 OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTILYMPHOM?
                 E CANCER/CT
                 E E27+ALL
                 E E30+ALL
L21              QUE ABB=ON  PLU=ON  CANCER+PFT,OLD,NEW,NT/CT
L22              QUE ABB=ON  PLU=ON  "CANCER (SYNDROME)"+PFT,OLD,NEW,NT/CT
L23              QUE ABB=ON  PLU=ON  NEOPLASM+PFT,OLD,NEW,NT/CT
                 E ANTINEOPLASTIC/CT
                 E E45+ALL
L24              QUE ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+PFT,OLD,NEW,NT/CT
                 E A61P0035-00/IPC
                 E E58+ALL
L25              QUE ABB=ON  PLU=ON  A61P0035/IPC OR A61P0035-00/IPC OR
                 A61P0035-02/IPC OR A61P0035-04/IPC

     FILE 'HCAPLUS' ENTERED AT 11:47:18 ON 30 NOV 2007
L*** DEL 345902 S L3
L26            28 SEA ABB=ON  PLU=ON  L13
L27        345902 SEA ABB=ON  PLU=ON  L3
L28          4251 SEA ABB=ON  PLU=ON  (L26 OR L27) (L) (L19 OR L20)
L29          3790 SEA ABB=ON  PLU=ON  L28 AND (L21 OR L22 OR L23 OR L24 OR L25)
L30          7141 SEA ABB=ON  PLU=ON  (L26 OR L27) (L) (THU OR PKT OR PAC OR DMA
                 OR BAC)/RL
L31           268 SEA ABB=ON  PLU=ON  L29 AND L30
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L32           4 SEA ABB=ON  PLU=ON  L31 AND (L14 OR L15 OR L16)
L33           1 SEA ABB=ON  PLU=ON  L1 AND L32
L34          23 SEA ABB=ON  PLU=ON  L30 AND L26
L35         286 SEA ABB=ON  PLU=ON  L31 OR L34
L36         282 SEA ABB=ON  PLU=ON  L35 NOT L32
L37         162 SEA ABB=ON  PLU=ON  L36 AND L17
L38          11 SEA ABB=ON  PLU=ON  L37 AND L26

     FILE 'REGISTRY' ENTERED AT 11:51:44 ON 30 NOV 2007
L39         870 SEA ABB=ON  PLU=ON  L7 AND NCSC2/ES

     FILE 'HCAPLUS' ENTERED AT 11:52:11 ON 30 NOV 2007
L40         328 SEA ABB=ON  PLU=ON  L39
L41           8 SEA ABB=ON  PLU=ON  L37 AND L40
L42          12 SEA ABB=ON  PLU=ON  L38 OR L41
                D SCAN TI HIT

     FILE 'STNGUIDE' ENTERED AT 11:53:15 ON 30 NOV 2007

     FILE 'HCAPLUS' ENTERED AT 11:54:39 ON 30 NOV 2007
L43         304 SEA ABB=ON  PLU=ON  (L26 OR L27) (L)((L19 OR L20)(L)(THU OR
                PKT OR PAC OR DMA OR BAC)/RL)
L44           0 SEA ABB=ON  PLU=ON  L43 AND 121-L25
L45         266 SEA ABB=ON  PLU=ON  L43 AND (L21 OR L22 OR L23 OR L24 OR L25)
L46           5 SEA ABB=ON  PLU=ON  L45 AND L26
L47           2 SEA ABB=ON  PLU=ON  L46 AND L40
L48         262 SEA ABB=ON  PLU=ON  L45 NOT L32
L49         150 SEA ABB=ON  PLU=ON  L48 AND L17
L50           1 SEA ABB=ON  PLU=ON  L49 AND L46
L51           0 SEA ABB=ON  PLU=ON  L49 AND L47
L52           8 SEA ABB=ON  PLU=ON  (L26 OR L40)(L)(L19 OR L20)
L53           2 SEA ABB=ON  PLU=ON  L49 AND L52
L54          23 SEA ABB=ON  PLU=ON  (L26 OR L40) AND (L21 OR L22 OR L23 OR L24
                OR L25)
L55           2 SEA ABB=ON  PLU=ON  L49 AND L54
L56         133 SEA ABB=ON  PLU=ON  L49 AND L24
L57          57 SEA ABB=ON  PLU=ON  L8
L58           1 SEA ABB=ON  PLU=ON  L49 AND L57

     FILE 'REGISTRY' ENTERED AT 12:02:41 ON 30 NOV 2007

     FILE 'HCAPLUS' ENTERED AT 12:02:47 ON 30 NOV 2007
L59             TRA PLU=ON  L56 1- RN :    6672 TERMS

     FILE 'REGISTRY' ENTERED AT 12:02:56 ON 30 NOV 2007
L60        6672 SEA ABB=ON  PLU=ON  L59
L61           2 SEA ABB=ON  PLU=ON  L7 AND L60
                D SCAN

     FILE 'HCAPLUS' ENTERED AT 12:04:46 ON 30 NOV 2007
L62           2 SEA ABB=ON  PLU=ON  L56 AND L61
                D SCAN TI HIT
L63           2 SEA ABB=ON  PLU=ON  (L50 OR L51) OR L53 OR L55 OR L58 OR L62
                D QUE L8
L64          18 SEA ABB=ON  PLU=ON  L57 AND (L19 OR L20 OR L21 OR L22 OR L23
                OR L24 OR L25)
L65          19 SEA ABB=ON  PLU=ON  L63 OR L64
L66          14 SEA ABB=ON  PLU=ON  L65 AND (L14 OR L15 OR L16)
L67          14 SEA ABB=ON  PLU=ON  L66 OR L32
L68           5 SEA ABB=ON  PLU=ON  L65 NOT L67
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L69           3 SEA ABB=ON  PLU=ON  L68 AND L17
                D SCAN TI HIT
                D BIB 1-3
L70         133 SEA ABB=ON  PLU=ON  L49 AND L24

     FILE 'REGISTRY' ENTERED AT 12:12:03 ON 30 NOV 2007
L71           1 SEA ABB=ON  PLU=ON  69-72-7/RN
                D SCAN

     FILE 'LREGISTRY' ENTERED AT 12:13:15 ON 30 NOV 2007
L72             STR L5

     FILE 'REGISTRY' ENTERED AT 12:15:17 ON 30 NOV 2007
L73          50 SEA SUB=L7 SSS SAM L72

     FILE 'LREGISTRY' ENTERED AT 12:15:47 ON 30 NOV 2007
L74             STR L72

     FILE 'REGISTRY' ENTERED AT 12:16:17 ON 30 NOV 2007
L75          50 SEA SUB=L7 SSS SAM L74

     FILE 'STNGUIDE' ENTERED AT 12:16:55 ON 30 NOV 2007
                D QUE STAT

     FILE 'REGISTRY' ENTERED AT 12:19:21 ON 30 NOV 2007
L76        1228 SEA SUB=L7 SSS FUL L74
                SAVE TEMP L76 RAE292RSET1/A

     FILE 'HCAPLUS' ENTERED AT 12:19:53 ON 30 NOV 2007
L77          11 SEA ABB=ON  PLU=ON  L76 (L)(L19 OR L20)
L78          29 SEA ABB=ON  PLU=ON  L76 AND (L21 OR L22 OR L23 OR L24 OR L25)
L79          30 SEA ABB=ON  PLU=ON  (L77 OR L78)
L80          10 SEA ABB=ON  PLU=ON  L79 AND (L14 OR L15 OR L16)
L81          20 SEA ABB=ON  PLU=ON  L79 NOT L80
L82          10 SEA ABB=ON  PLU=ON  L81 AND L17

     FILE 'REGISTRY' ENTERED AT 12:21:52 ON 30 NOV 2007

     FILE 'LREGISTRY' ENTERED AT 12:21:57 ON 30 NOV 2007

     FILE 'REGISTRY' ENTERED AT 12:22:08 ON 30 NOV 2007
L83         184 SEA ABB=ON  PLU=ON  L4 AND L76

     FILE 'HCAPLUS' ENTERED AT 12:22:48 ON 30 NOV 2007

     FILE 'STNGUIDE' ENTERED AT 12:22:59 ON 30 NOV 2007

     FILE 'HCAPLUS' ENTERED AT 12:24:26 ON 30 NOV 2007
L84          10 SEA ABB=ON  PLU=ON  L82 OR L50 OR L51 OR L53 OR L55 OR L58 OR
                L69
                D SCAN TI HIT

     FILE 'STNGUIDE' ENTERED AT 12:25:34 ON 30 NOV 2007

     FILE 'HCAPLUS' ENTERED AT 12:26:06 ON 30 NOV 2007
L85          10 SEA ABB=ON  PLU=ON  L80 AND (L14 OR L15 OR L16)

     FILE 'STNGUIDE' ENTERED AT 12:26:16 ON 30 NOV 2007

     FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 12:26:19 ON 30 NOV 2007
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     FILE 'REGISTRY' ENTERED AT 12:26:21 ON 30 NOV 2007
L86          549 SEA ABB=ON  PLU=ON  L76 AND (USPATFULL OR USPAT2 OR USPATOLD)/L
                 C

     FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 12:26:46 ON 30 NOV 2007
L87          126 SEA ABB=ON  PLU=ON  L86
L88            2 SEA ABB=ON  PLU=ON  L87 AND L25
L89            2 SEA ABB=ON  PLU=ON  L88 AND (L19/IT,TI,CC,CT,ST,STP OR
                 L20/IT,TI,CC,CT,ST,STP)
L90            2 SEA ABB=ON  PLU=ON  (L88 OR L89)
L91           13 SEA ABB=ON  PLU=ON  L87 AND (L14 OR L15 OR L16)
L92            0 SEA ABB=ON  PLU=ON  L90 NOT L91

     FILE 'REGISTRY' ENTERED AT 12:27:46 ON 30 NOV 2007
L93            1 SEA ABB=ON  PLU=ON  L13 AND L76
L94            0 SEA ABB=ON  PLU=ON  L13 NOT L76

     FILE 'STNGUIDE' ENTERED AT 12:28:02 ON 30 NOV 2007

     FILE 'WPIX' ENTERED AT 12:28:13 ON 30 NOV 2007

     FILE 'STNGUIDE' ENTERED AT 12:28:50 ON 30 NOV 2007

     FILE 'WPIX' ENTERED AT 12:29:38 ON 30 NOV 2007
L95              QUE ABB=ON  PLU=ON  (B14-H01 OR C14-H01 OR B14-H01? OR
                 C14-H01?)/MC
L96           11 SEA SSS SAM L74
                 D TRI 1-11
                 D QUE STAT
L97          104 SEA SSS FUL L74
                 SAVE TEMP L97 RAE292WPIS/A
L98           32 SEA ABB=ON  PLU=ON  L97/DCR
                 SELECT L97 1- SDCN
L99           32 SEA ABB=ON  PLU=ON  (RAAFWU/DCN OR RACQNZ/DCN OR RACQX0/DCN OR
                 RACRDB/DCN OR RACRDC/DCN OR RACRDD/DCN OR RACRDE/DCN OR
                 RACRDF/DCN OR RACRDG/DCN OR RACRDH/DCN OR RACRDI/DCN OR
                 RACRDJ/DCN OR RACRDK/DCN OR RACRDL/DCN OR RACRDM/DCN OR
                 RACRDN/DCN OR RACRDO/DCN OR RACRDP/DCN OR RACRDQ/DCN OR
                 RACRDR/DCN OR RACRDS/DCN OR RACRDT/DCN OR RACRDV/DCN OR
                 RACRDX/DCN OR RACRDY/DCN OR RACRDZ/DCN OR RACRE0/DCN OR
                 RACRE1/DCN OR RACRE2/DCN OR RACRRD/DCN OR RACRRE/DCN OR
                 RACRRF/DCN OR RACVTE/DCN OR RACVTF/DCN OR RACVTK/DCN OR
                 RACVTM/DCN OR RACVTN/DCN OR RACVTO/DCN OR RACVTP/DCN OR
                 RACVTQ/DCN OR RACVTT/DCN OR RACVTU/DCN OR RACVTV/DCN OR
                 RACVTW/DCN OR RACVTX/DCN OR RACVTY/DCN OR RACVTZ/DCN OR
                 RACVU0/DCN OR RACVU1/DCN OR RACVU2/DCN OR RACVU3/DCN OR
                 RACVU4/DCN OR RACWGE/DCN OR RACWGF/DCN OR RAC72I/DCN OR
                 RAGUJA/DCN OR RAGUJB/DCN OR RAGUJC/DCN OR RAGUJD/DCN OR
                 RAGUJE/DCN OR RAGUJF/DCN OR RAGUJG/DCN OR RAGUJH/DCN OR
                 RAGUJI/DCN OR RAGUJJ/DCN OR RAGUJK/DCN OR RAGUJL/DCN OR
                 RAGUJM/DCN OR RAGUJN/DCN OR RAGUJO/DCN OR RAHG3A/DCN OR
                 RAIX7Z/DCN OR RAMFVC/DCN OR RAM4LO/DCN OR RAM4LP/DCN OR
                 RAM4LQ/DCN OR RAM4LR/DCN OR RAM4LS/DCN OR RAM4LT/DCN OR
                 RANL8F/DCN OR RANL8G/DCN OR RANL8H/DCN OR RANL8I/DCN OR
                 RANL8R/DCN OR RANL8S/DCN OR RANL8T/DCN OR RANL8U/DCN OR
                 RAN3RR/DCN OR RAN3RU/DCN OR RAN3RV/DCN OR RAOIRH/DCN OR
                 RAOIRI/DCN OR RAOIRJ/DCN OR RAOIRL/DCN OR RAOIRM/DCN OR
                 RAPE56/DCN OR RA0F6S/DCN OR RA0F6T/DCN OR RA0F6U/DCN OR
                 RA0F71/DCN OR RA0F72/DCN OR RA0F73/DCN OR RA5NA8/DCN OR
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                RA75IT/DCN)
L100          32 SEA ABB=ON  PLU=ON  (L98 OR L99)
L101          10 SEA ABB=ON  PLU=ON  L100 AND (L95 OR L25 OR (P633 OR P631 OR
                P632)/M0,M1,M2,M3,M4,M5,M6)
L102          10 SEA ABB=ON  PLU=ON  L100 AND (L19 OR L20)
L103          10 SEA ABB=ON  PLU=ON  L101 AND L102
L104          10 SEA ABB=ON  PLU=ON  (L101 OR L102 OR L103)
L105           6 SEA ABB=ON  PLU=ON  L104 AND (L14 OR L15 OR L16)
L106           4 SEA ABB=ON  PLU=ON  L104 NOT L105
L107           0 SEA ABB=ON  PLU=ON  L106 AND L18

     FILE 'STNGUIDE' ENTERED AT 12:34:48 ON 30 NOV 2007
                D SAVED

     FILE 'REGISTRY' ENTERED AT 12:35:18 ON 30 NOV 2007
L108        1228 SEA ABB=ON  PLU=ON  L13 OR L76
L109           1 SEA ABB=ON  PLU=ON  L108 AND MEDLINE/LC

     FILE 'MEDLINE' ENTERED AT 12:35:41 ON 30 NOV 2007
L110         124 SEA ABB=ON  PLU=ON  L109
                E ANTINEOPLAS/CT
L111            QUE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENTS"+PFT,OLD,NEW,NT/CT
                E ANTITUMOR AGENTS/CT
L112          22 SEA ABB=ON  PLU=ON  L110 AND (L111 OR (L19 OR L20))
L113           0 SEA ABB=ON  PLU=ON  L112 AND (L14 OR L15 OR L16)
L*** DEL       0 S L113 NOT L112
L114          22 SEA ABB=ON  PLU=ON  L112 NOT L113
L115          11 SEA ABB=ON  PLU=ON  L114 AND L17
                D TRI 6-11

     FILE 'REGISTRY' ENTERED AT 12:38:06 ON 30 NOV 2007
                D SCAN L109
                D IDE L109
L116           6 SEA ABB=ON  PLU=ON  L108 AND EMBASE/LC

     FILE 'EMBASE' ENTERED AT 12:39:52 ON 30 NOV 2007
L117         337 SEA ABB=ON  PLU=ON  L116
                E ANTINEOPLASTIC/CT
L118            QUE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+PFT,OLD,NEW,NT/CT
L119          77 SEA ABB=ON  PLU=ON  L117 AND (L118 OR (L19 OR L20))
L120           0 SEA ABB=ON  PLU=ON  L119 AND (L14 OR L15 OR L16)
L121          77 SEA ABB=ON  PLU=ON  L119 NOT L120
L122          55 SEA ABB=ON  PLU=ON  L121 AND L17
                D TRI 50-55
L123            QUE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+PFT,OLD,NEW/CT
L124            QUE ABB=ON  PLU=ON  "CANCER INHIBITION"+PFT,OLD,NEW,NT/CT
L125          25 SEA ABB=ON  PLU=ON  L122 AND (L19 OR L20)
L126          44 SEA ABB=ON  PLU=ON  L122 AND (L123 OR L124)
L127          55 SEA ABB=ON  PLU=ON  (L125 OR L126)
L128          25 SEA ABB=ON  PLU=ON  L127 AND L125
                D TRI 20-22
L129         265 SEA ABB=ON  PLU=ON  NITAZOXANIDE+PFT,OLD,NEW,NT/CT (L) DT/CT
L130          45 SEA ABB=ON  PLU=ON  L127 AND L129
                D TRI 40
                E NEOPLASM/CT
L131            QUE ABB=ON  PLU=ON  NEOPLASM+PFT,OLD,NEW,NT/CT
                E TUMOR/CT
L132            QUE ABB=ON  PLU=ON  TUMOR+PFT,OLD,NEW,NT/CT
L133      240317 SEA ABB=ON  PLU=ON  (L131 OR L132) (L) DT/CT
                D TRI
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L134            6 SEA ABB=ON  PLU=ON  L127 AND L133
L135            6 SEA ABB=ON  PLU=ON  L134 NOT L120
L136            6 SEA ABB=ON  PLU=ON  L135 AND L17
                  D TRI 1-6

     FILE 'STNGUIDE' ENTERED AT 12:47:30 ON 30 NOV 2007

     FILE 'EMBASE' ENTERED AT 12:48:32 ON 30 NOV 2007
L137            5 SEA ABB=ON  PLU=ON  L130 AND L133
L138            6 SEA ABB=ON  PLU=ON  L136 OR L137
L139            6 SEA ABB=ON  PLU=ON  L138 NOT L120
L140            6 SEA ABB=ON  PLU=ON  L139 AND L17

     FILE 'STNGUIDE' ENTERED AT 12:49:30 ON 30 NOV 2007

     FILE 'REGISTRY' ENTERED AT 12:49:32 ON 30 NOV 2007
L*** DEL        0 S L108 AND (BIOSIS OR CABA OR BIOTECHNO OR DRUGU OR VETU)/LS
L141            4 SEA ABB=ON  PLU=ON  L108 AND (BIOSIS OR CABA OR BIOTECHNO OR
                  DRUGU OR VETU)/LC

     FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 12:50:14 ON 30 NOV
     2007
L142          210 SEA ABB=ON  PLU=ON  L141
L143           12 SEA ABB=ON  PLU=ON  L142 AND (L19 OR L20)
L144            0 SEA ABB=ON  PLU=ON  L143 AND (L14 OR L15 OR L16)
L145           12 SEA ABB=ON  PLU=ON  L143 NOT L144
L146            6 SEA ABB=ON  PLU=ON  L145 AND L17
                  D SCAN

     FILE 'STNGUIDE' ENTERED AT 12:52:05 ON 30 NOV 2007

     FILE 'REGISTRY' ENTERED AT 12:52:11 ON 30 NOV 2007
L147            9 SEA ABB=ON  PLU=ON  L13 OR L109 OR L116 OR L141

     FILE 'MEDLINE, BIOSIS, EMBASE, PASCAL, LIFESCI, BIOENG, CABA, AGRICOLA,
     BIOTECHNO, BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI,
     DISSABS' ENTERED AT 12:53:14 ON 30 NOV 2007

     FILE 'REGISTRY' ENTERED AT 12:53:24 ON 30 NOV 2007
                  SET SMARTSELECT ON
L148              SEL PLU=ON  L147 1- NAME :      24 TERMS
                  SET SMARTSELECT OFF

     FILE 'MEDLINE, BIOSIS, EMBASE, PASCAL, LIFESCI, BIOENG, CABA, AGRICOLA,
     BIOTECHNO, BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI,
     DISSABS' ENTERED AT 12:53:26 ON 30 NOV 2007
L149         7188 SEA ABB=ON  PLU=ON  L148
L150         1006 SEA ABB=ON  PLU=ON  L149 AND (L19 OR L20)
L151           33 SEA ABB=ON  PLU=ON  L150 AND (L14 OR L15 OR L16)
L152            0 SEA ABB=ON  PLU=ON  L151 NOT L150
L153          973 SEA ABB=ON  PLU=ON  L150 NOT L151
L154          723 SEA ABB=ON  PLU=ON  L153 AND (L19/IT,TI,CC,CT,ST,STP OR
                  L20/IT,TI,CC,CT,ST,STP)
L155         1878 SEA ABB=ON  PLU=ON  L148/IT,TI,CC,CT,ST,STP
L156          153 SEA ABB=ON  PLU=ON  L154 AND L155
L157           60 SEA ABB=ON  PLU=ON  L156 AND L17
L158           46 SEA ABB=ON  PLU=ON  L157 AND (CLINIC? OR THERAP? OR TREAT? OR
                  MEDIC? OR CHEMOTHERAP?)/IT,TI,CC,CT,ST,STP
L159            9 SEA ABB=ON  PLU=ON  L158 AND (L149 (10A) (TREAT? OR THERAP?))
```

```
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 13:17:45 ON 30 NOV 2007
                D QUE STAT L7
                D QUE STAT L13
                D QUE STAT L76
                D QUE NOS L108
                D QUE NOS L84
                D QUE NOS L92
                D QUE STAT L97
                D QUE L107
                D QUE NOS L115
                D QUE NOS L140
                D QUE NOS L146
                D QUE NOS L159

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, BIOTECHNO, DRUGU, SCISEARCH'
     ENTERED AT 13:20:50 ON 30 NOV 2007
L160          40 DUP REM L84 L92 L107 L115 L140 L146 L159 (2 DUPLICATES REMOVED
                     ANSWERS '1-10' FROM FILE HCAPLUS
                     ANSWERS '11-21' FROM FILE MEDLINE
                     ANSWERS '22-28' FROM FILE EMBASE
                     ANSWERS '29-32' FROM FILE BIOSIS
                     ANSWER '33' FROM FILE BIOTECHNO
                     ANSWERS '34-39' FROM FILE DRUGU
                     ANSWER '40' FROM FILE SCISEARCH
                SAVE TEMP L160 RAE292MAIN/A

     FILE 'STNGUIDE' ENTERED AT 13:21:06 ON 30 NOV 2007

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, BIOTECHNO, DRUGU, SCISEARCH'
     ENTERED AT 13:21:27 ON 30 NOV 2007
                D IBIB ED ABS HITIND HITSTR

     FILE 'STNGUIDE' ENTERED AT 13:21:34 ON 30 NOV 2007

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, BIOTECHNO, DRUGU, SCISEARCH'
     ENTERED AT 13:22:53 ON 30 NOV 2007
                D IBIB ED ABS HITIND HITSTR 2-10

     FILE 'STNGUIDE' ENTERED AT 13:23:01 ON 30 NOV 2007

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, BIOTECHNO, DRUGU, SCISEARCH'
     ENTERED AT 13:26:15 ON 30 NOV 2007
                D IBIB ED AB IND 11-40

     FILE 'STNGUIDE' ENTERED AT 13:26:21 ON 30 NOV 2007

     FILE 'STNGUIDE' ENTERED AT 13:51:34 ON 30 NOV 2007
                D QUE NOS L80
                D QUE NOS L91
                D QUE NOS L105
                D QUE NOS L113
                D QUE NOS L120
                D QUE NOS L144
                D QUE NOS L151

     FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, EMBASE, PASCAL, LIFESCI,
     DRUGU, SCISEARCH' ENTERED AT 13:53:06 ON 30 NOV 2007
L161          34 DUP REM L80 L91 L105 L113 L120 L144 L151 (28 DUPLICATES REMOVE
```

ANSWERS '1-10' FROM FILE HCAPLUS
ANSWERS '11-23' FROM FILE USPATFULL
ANSWERS '24-27' FROM FILE WPIX
ANSWERS '28-29' FROM FILE MEDLINE
ANSWERS '30-31' FROM FILE BIOSIS
ANSWER '32' FROM FILE PASCAL
ANSWERS '33-34' FROM FILE DRUGU
SAVE TEMP L161 RAE292INV/A

FILE 'STNGUIDE' ENTERED AT 13:53:27 ON 30 NOV 2007

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, PASCAL, DRUGU' ENTERED AT 13:53:55 ON 30 NOV 2007
D IBIB ED ABS HITIND HITSTR

FILE 'STNGUIDE' ENTERED AT 13:53:56 ON 30 NOV 2007

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, PASCAL, DRUGU' ENTERED AT 13:54:06 ON 30 NOV 2007
D IBIB ED ABS HITIND HITSTR 2-10

FILE 'STNGUIDE' ENTERED AT 13:54:39 ON 30 NOV 2007

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, PASCAL, DRUGU' ENTERED AT 13:55:27 ON 30 NOV 2007
D IBIB AB HITSTR 11-23

FILE 'STNGUIDE' ENTERED AT 13:56:26 ON 30 NOV 2007

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, PASCAL, DRUGU' ENTERED AT 13:57:00 ON 30 NOV 2007
D IALL ABEQ TECH ABEX HITSTR 24-27

FILE 'STNGUIDE' ENTERED AT 13:57:09 ON 30 NOV 2007

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, PASCAL, DRUGU' ENTERED AT 13:57:32 ON 30 NOV 2007
D IBIB AB 28-34

FILE 'STNGUIDE' ENTERED AT 13:57:33 ON 30 NOV 2007

FILE 'STNGUIDE' ENTERED AT 13:57:40 ON 30 NOV 2007

FILE HOME

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 23, 2007 (20071123/UP).

FILE ZCAPLUS

```
=> => d que nos 180
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L21             QUE  ABB=ON  PLU=ON  CANCER+PFT,OLD,NEW,NT/CT
L22             QUE  ABB=ON  PLU=ON  "CANCER (SYNDROME)"+PFT,OLD,NEW,NT/C
                T
L23             QUE  ABB=ON  PLU=ON  NEOPLASM+PFT,OLD,NEW,NT/CT
L24             QUE  ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+PFT,OLD,NEW,NT/CT
L25             QUE  ABB=ON  PLU=ON  A61P0035/IPC OR A61P0035-00/IPC OR A
                61P0035-02/IPC OR A61P0035-04/IPC
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L77          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L76 (L)(L19 OR L20)
L78          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L76 AND (L21 OR L22 OR L23 OR
                L24 OR L25)
L79          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L77 OR L78)
L80          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L79 AND (L14 OR L15 OR L16)


=> d his l91

     (FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 12:26:46 ON 30 NOV 2007)
L91          13 S L87 AND L14-L16

=> d que nos l91
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L74             STR
L76        1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L86         549 SEA FILE=REGISTRY ABB=ON  PLU=ON  L76 AND (USPATFULL OR USPAT2
                OR USPATOLD)/LC
L87         126 SEA L86
L91          13 SEA L87 AND (L14 OR L15 OR L16)


=> d que nos l105
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
```

```
                LYMPHOM?
L25             QUE  ABB=ON  PLU=ON  A61P0035/IPC OR A61P0035-00/IPC OR A
                61P0035-02/IPC OR A61P0035-04/IPC
L74             STR
L95             QUE  ABB=ON  PLU=ON  (B14-H01 OR C14-H01 OR B14-H01? OR C
                14-H01?)/MC
L97         104 SEA FILE=WPIX SSS FUL L74
L98          32 SEA FILE=WPIX ABB=ON  PLU=ON  L97/DCR
L99          32 SEA FILE=WPIX ABB=ON  PLU=ON  (RAAFWU/DCN OR RACQNZ/DCN OR
                RACQX0/DCN OR RACRDB/DCN OR RACRDC/DCN OR RACRDD/DCN OR
                RACRDE/DCN OR RACRDF/DCN OR RACRDG/DCN OR RACRDH/DCN OR
                RACRDI/DCN OR RACRDJ/DCN OR RACRDK/DCN OR RACRDL/DCN OR
                RACRDM/DCN OR RACRDN/DCN OR RACRDO/DCN OR RACRDP/DCN OR
                RACRDQ/DCN OR RACRDR/DCN OR RACRDS/DCN OR RACRDT/DCN OR
                RACRDV/DCN OR RACRDX/DCN OR RACRDY/DCN OR RACRDZ/DCN OR
                RACRE0/DCN OR RACRE1/DCN OR RACRE2/DCN OR RACRRD/DCN OR
                RACRRE/DCN OR RACRRF/DCN OR RACVTE/DCN OR RACVTF/DCN OR
                RACVTK/DCN OR RACVTM/DCN OR RACVTN/DCN OR RACVTO/DCN OR
                RACVTP/DCN OR RACVTQ/DCN OR RACVTT/DCN OR RACVTU/DCN OR
                RACVTV/DCN OR RACVTW/DCN OR RACVTX/DCN OR RACVTY/DCN OR
                RACVTZ/DCN OR RACVU0/DCN OR RACVU1/DCN OR RACVU2/DCN OR
                RACVU3/DCN OR RACVU4/DCN OR RACWGE/DCN OR RACWGF/DCN OR
                RAC72I/DCN OR RAGUJA/DCN OR RAGUJB/DCN OR RAGUJC/DCN OR
                RAGUJD/DCN OR RAGUJE/DCN OR RAGUJF/DCN OR RAGUJG/DCN OR
                RAGUJH/DCN OR RAGUJI/DCN OR RAGUJJ/DCN OR RAGUJK/DCN OR
                RAGUJL/DCN OR RAGUJM/DCN OR RAGUJN/DCN OR RAGUJO/DCN OR
                RAHG3A/DCN OR RAIX7Z/DCN OR RAMFVC/DCN OR RAM4LO/DCN OR
                RAM4LP/DCN OR RAM4LQ/DCN OR RAM4LR/DCN OR RAM4LS/DCN OR
                RAM4LT/DCN OR RANL8F/DCN OR RANL8G/DCN OR RANL8H/DCN OR
                RANL8I/DCN OR RANL8R/DCN OR RANL8S/DCN OR RANL8T/DCN OR
                RANL8U/DCN OR RAN3RR/DCN OR RAN3RU/DCN OR RAN3RV/DCN OR
                RAOIRH/DCN OR RAOIRI/DCN OR RAOIRJ/DCN OR RAOIRL/DCN OR
                RAOIRM/DCN OR RAPE56/DCN OR RA0F6S/DCN OR RA0F6T/DCN OR
                RA0F6U/DCN OR RA0F71/DCN OR RA0F72/DCN OR RA0F73/DCN OR
                RA5NA8/DCN OR RA75IT/DCN)
L100         32 SEA FILE=WPIX ABB=ON  PLU=ON  (L98 OR L99)
L101         10 SEA FILE=WPIX ABB=ON  PLU=ON  L100 AND (L95 OR L25 OR (P633 OR
                P631 OR P632)/M0,M1,M2,M3,M4,M5,M6)
L102         10 SEA FILE=WPIX ABB=ON  PLU=ON  L100 AND (L19 OR L20)
L103         10 SEA FILE=WPIX ABB=ON  PLU=ON  L101 AND L102
L104         10 SEA FILE=WPIX ABB=ON  PLU=ON  (L101 OR L102 OR L103)
L105          6 SEA FILE=WPIX ABB=ON  PLU=ON  L104 AND (L14 OR L15 OR L16)


=> d que nos l113
L1            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4          561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7         2808 SEA FILE=REGISTRY SSS FUL L5
L8          187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9           10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14             QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15             QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16             QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19             QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
```

```
                OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                N?
L20             QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                LYMPHOM?
L74             STR
L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108        1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L109           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND MEDLINE/LC
L110         124 SEA FILE=MEDLINE ABB=ON  PLU=ON  L109
L111            QUE  ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENTS"+PFT,OLD,NEW,
                NT/CT
L112          22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L110 AND (L111 OR (L19 OR
                L20))
L113           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L112 AND (L14 OR L15 OR L16)


=> d que nos l120
L1              1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3                TRANSFER  PLU=ON  L1 1- RN :     561 TERMS
L4            561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5                STR
L7           2808 SEA FILE=REGISTRY SSS FUL L5
L8            187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9             10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12             3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                O2"/MF
L14               QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15               QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16               QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19               QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                  OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                  MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                  N?
L20               QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                  OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                  LYMPHOM?
L74               STR
L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108        1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L116           6 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND EMBASE/LC
L117         337 SEA FILE=EMBASE ABB=ON  PLU=ON  L116
L118            QUE  ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+PFT,OLD,NEW,N
                T/CT
L119          77 SEA FILE=EMBASE ABB=ON  PLU=ON  L117 AND (L118 OR (L19 OR
                L20))
L120           0 SEA FILE=EMBASE ABB=ON  PLU=ON  L119 AND (L14 OR L15 OR L16)


=> d his l144

     (FILE 'BIOSIS, CABA, BIOTECHNO, DRUGU, VETU' ENTERED AT 12:50:14 ON 30
     NOV 2007)
L144           0 S L143 AND L14-L16

=> d que nos l144
L1              1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
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```
L3              TRANSFER  PLU=ON  L1 1- RN :      561 TERMS
L4           561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7          2808 SEA FILE=REGISTRY SSS FUL L5
L8           187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9            10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                 YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                 O2"/MF
L14              QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15              QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16              QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19              QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                 OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                 MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                 N?
L20              QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                 OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                 LYMPHOM?
L74              STR
L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108        1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L141           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND (BIOSIS OR CABA OR
                 BIOTECHNO OR DRUGU OR VETU)/LC
L142         210 SEA L141
L143          12 SEA L142 AND (L19 OR L20)
L144           0 SEA L143 AND (L14 OR L15 OR L16)


=> d his l151

     (FILE 'MEDLINE, BIOSIS, EMBASE, PASCAL, LIFESCI, BIOENG, CABA, AGRICOLA,
     BIOTECHNO, BIOTECHDS, DRUGU, DRUGB, VETU, VETB, SCISEARCH, CONFSCI,
     DISSABS' ENTERED AT 12:53:26 ON 30 NOV 2007)
L151           33 S L150 AND L14-L16

=> d que nos l151
L1              1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005-516292/APPS
L3              TRANSFER  PLU=ON  L1 1- RN :      561 TERMS
L4           561 SEA FILE=REGISTRY ABB=ON  PLU=ON  L3
L5              STR
L7          2808 SEA FILE=REGISTRY SSS FUL L5
L8           187 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND L7
L9            10 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND 6/F AND 1/CL
L12            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND "3,5-BIS(TRIFLUOROMETH
                 YL)PHENYL"/CNS AND "5-CHLORO-2-HYDROXY"/CNS
L13            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND "C15 H8 CL F6 N
                 O2"/MF
L14              QUE  ABB=ON  PLU=ON  MUTO, S?/AU
L15              QUE  ABB=ON  PLU=ON  ITAI, A?/AU
L16              QUE  ABB=ON  PLU=ON  (MEDICINAL (W) MOLECULAR)/CS,SO,PA
L19              QUE  ABB=ON  PLU=ON  ?CANCER? OR ?CARCIN? OR ONCO? OR ?NE
                 OPLAS? OR ?TUMOR? OR ?TUMOUR? OR MALIGN? OR ?SARCOM? OR ?
                 MELANOM? OR ?LEUKEM? OR ?LEUKAEM? OR ?LYMPHOM? OR ?HODGKI
                 N?
L20              QUE  ABB=ON  PLU=ON  ANTICANCER? OR ANTICARCIN? OR ANTINE
                 OPLAS? OR ANTITUM? OR ANTISARCOM? OR ANTIMELANOM? OR ANTI
                 LYMPHOM?
L74              STR
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L76         1228 SEA FILE=REGISTRY SUB=L7 SSS FUL L74
L108        1228 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L76
L109           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND MEDLINE/LC
L116           6 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND EMBASE/LC
L141           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L108 AND (BIOSIS OR CABA OR
                 BIOTECHNO OR DRUGU OR VETU)/LC
L147           9 SEA FILE=REGISTRY ABB=ON  PLU=ON  L13 OR L109 OR L116 OR L141
L148             SEL  PLU=ON  L147 1- NAME :      24 TERMS
L149        7188 SEA L148
L150        1006 SEA L149 AND (L19 OR L20)
L151          33 SEA L150 AND (L14 OR L15 OR L16)


=> dup rem l80 l91 l105 l113 l120 l144 l151
L113 HAS NO ANSWERS
L120 HAS NO ANSWERS
L144 HAS NO ANSWERS
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PROCESSING COMPLETED FOR L91
PROCESSING COMPLETED FOR L105
PROCESSING COMPLETED FOR L113
PROCESSING COMPLETED FOR L120
PROCESSING COMPLETED FOR L144
PROCESSING COMPLETED FOR L151
L161          34 DUP REM L80 L91 L105 L113 L120 L144 L151 (28 DUPLICATES REMOVED)
                 ANSWERS '1-10' FROM FILE HCAPLUS
                 ANSWERS '11-23' FROM FILE USPATFULL
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                ANSWERS '24-27' FROM FILE WPIX
                ANSWERS '28-29' FROM FILE MEDLINE
                ANSWERS '30-31' FROM FILE BIOSIS
                ANSWER '32' FROM FILE PASCAL
                ANSWERS '33-34' FROM FILE DRUGU

=> file stnguide
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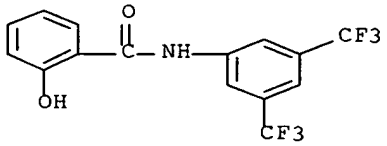
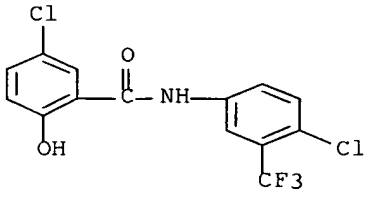
634186-92-8 634186-93-9 634186-96-2
634186-97-3 634186-99-5 634187-00-1
634187-01-2 634189-16-5

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(trifluoromethylphenylchlorohydroxybenzamide analogs as chromatosis and skin **cancer** remedies and skin whitening cosmetics)

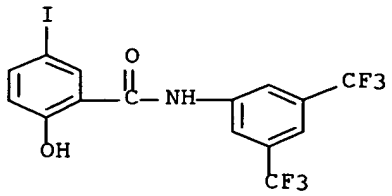
RN 744-58-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy- (9CI) (CA INDEX NAME)



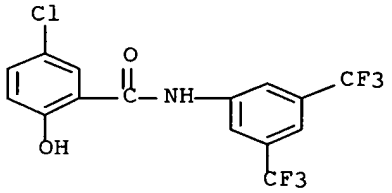

RN 900-36-7 HCAPLUS
CN Benzamide, 5-chloro-N-[4-chloro-3-(trifluoromethyl)phenyl]-2-hydroxy- (9CI) (CA INDEX NAME)



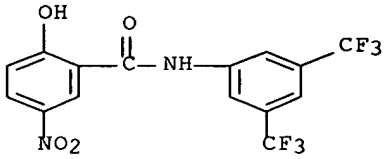
RN 906-38-7 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-iodo- (9CI) (CA INDEX NAME)



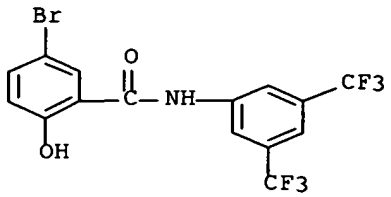
RN 978-62-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxy- (CA INDEX NAME)



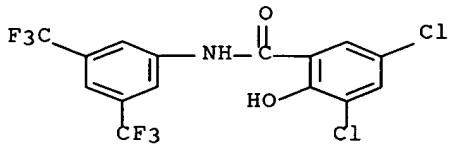
RN 982-71-8 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-nitro- (9CI) (CA INDEX NAME)



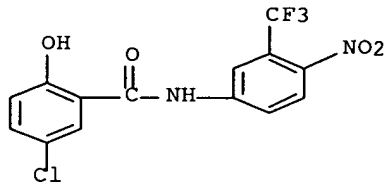
RN 3823-84-5 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-bromo-2-hydroxy- (9CI) (CA INDEX NAME)



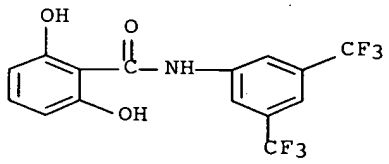
RN 4554-46-5 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-3,5-dichloro-2-hydroxy- (9CI) (CA INDEX NAME)



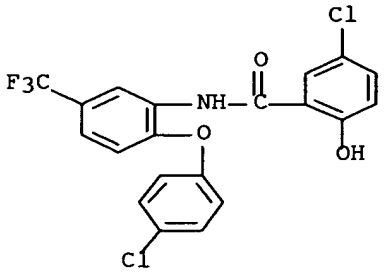
RN 16739-23-4 HCAPLUS
CN Benzamide, 5-chloro-2-hydroxy-N-[4-nitro-3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



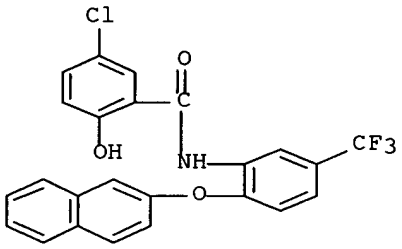
RN 31912-59-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2,6-dihydroxy- (9CI) (CA INDEX NAME)



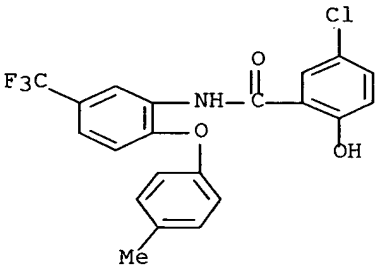
RN 73662-28-9 HCAPLUS
CN Benzamide, 5-chloro-N-[2-(4-chlorophenoxy)-5-(trifluoromethyl)phenyl]-2-hydroxy- (9CI) (CA INDEX NAME)



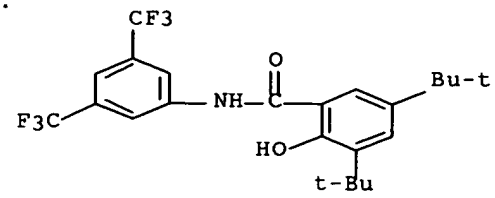
RN 73662-32-5 HCAPLUS
CN Benzamide, 5-chloro-2-hydroxy-N-[2-(2-naphthalenyloxy)-5-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



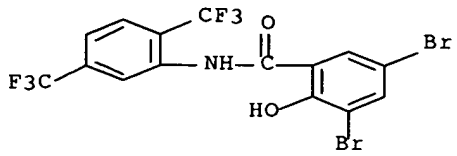
RN 79567-27-4 HCAPLUS
CN Benzamide, 5-chloro-2-hydroxy-N-[2-(4-methylphenoxy)-5-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



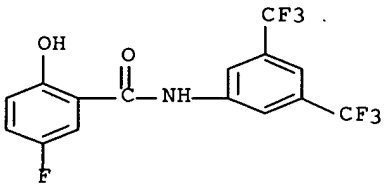
RN 192049-18-6 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-3,5-bis(1,1-dimethylethyl)-2-hydroxy- (CA INDEX NAME)



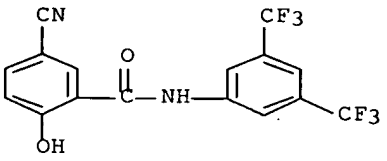
RN 313495-77-1 HCAPLUS
CN Benzamide, N-[2,5-bis(trifluoromethyl)phenyl]-3,5-dibromo-2-hydroxy- (CA INDEX NAME)



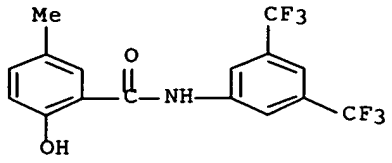
RN 439144-17-9 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-fluoro-2-hydroxy- (CA INDEX NAME)



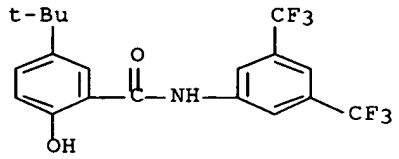
RN 439144-18-0 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-cyano-2-hydroxy- (CA INDEX NAME)



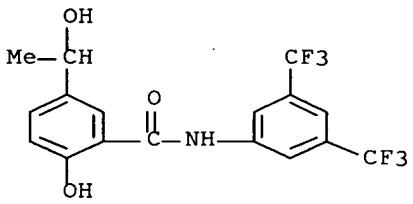
RN 439144-19-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-methyl- (CA INDEX NAME)



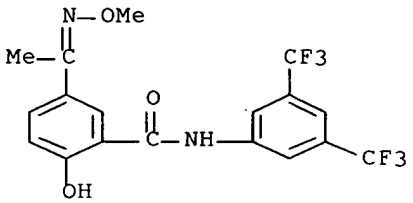
RN 439144-20-4 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-(1,1-dimethylethyl)-2-hydroxy- (CA INDEX NAME)



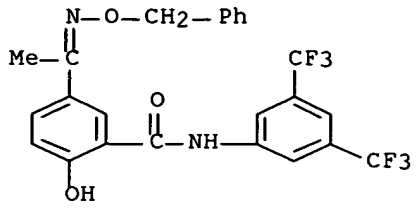
RN 439144-21-5 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(1-hydroxyethyl)- (CA INDEX NAME)



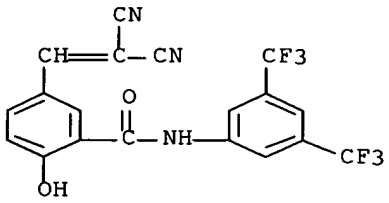
RN 439144-22-6 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[1-(methoxyimino)ethyl]- (CA INDEX NAME)



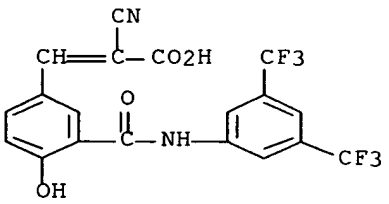
RN 439144-23-7 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[1-[(phenylmethoxy)imino]ethyl]- (CA INDEX NAME)



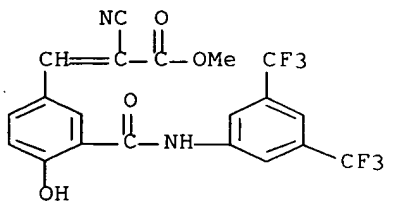
RN 439144-24-8 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-(2,2-dicyanoethenyl)-2-hydroxy- (CA INDEX NAME)



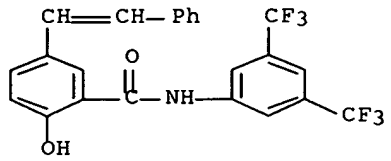
RN 439144-25-9 HCAPLUS
CN 2-Propenoic acid, 3-[3-[[[3,5-bis(trifluoromethyl)phenyl]amino]carbonyl]-4-hydroxyphenyl]-2-cyano- (CA INDEX NAME)



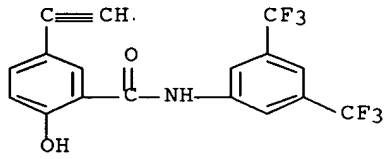
RN 439144-26-0 HCAPLUS
CN 2-Propenoic acid, 3-[3-[[[3,5-bis(trifluoromethyl)phenyl]amino]carbonyl]-4-hydroxyphenyl]-2-cyano-, methyl ester (CA INDEX NAME)



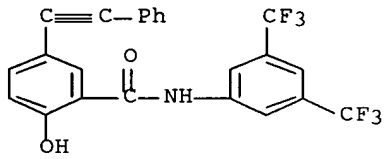
RN 439144-27-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-phenylethenyl)- (CA INDEX NAME)



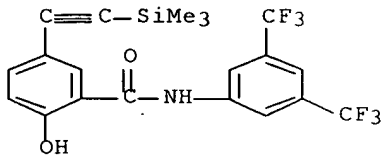
RN 439144-28-2 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-ethynyl-2-hydroxy- (CA INDEX NAME)



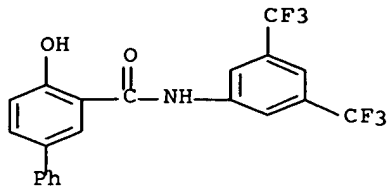
RN 439144-29-3 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(phenylethynyl)- (9CI) (CA INDEX NAME)



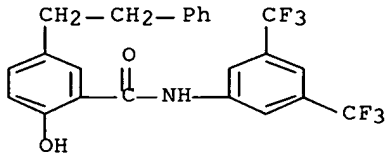
RN 439144-30-6 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[(trimethylsilyl)ethynyl]- (9CI) (CA INDEX NAME)



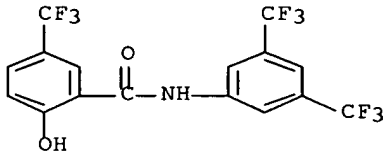
RN 439144-31-7 HCAPLUS
CN [1,1'-Biphenyl]-3-carboxamide, N-[3,5-bis(trifluoromethyl)phenyl]-4-hydroxy- (CA INDEX NAME)



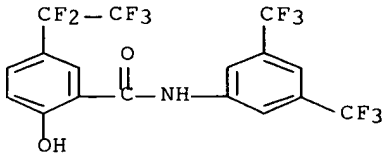
RN 439144-32-8 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-phenylethyl)- (CA INDEX NAME)



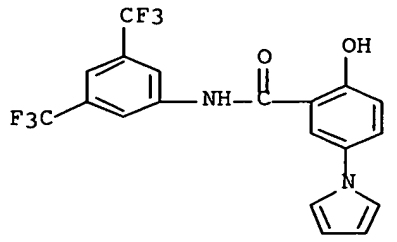
RN 439144-33-9 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(trifluoromethyl)- (CA INDEX NAME)



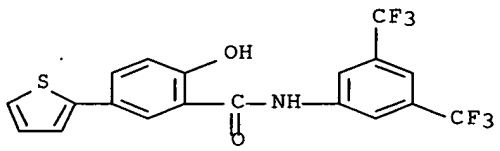
RN 439144-34-0 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(pentafluoroethyl)- (9CI) (CA INDEX NAME)



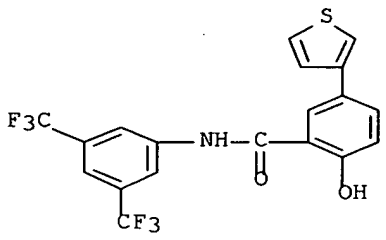
RN 439144-35-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(1H-pyrrol-1-yl)- (CA INDEX NAME)



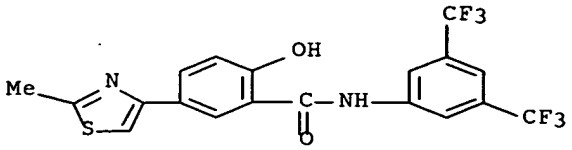
RN 439144-37-3 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-thienyl)- (CA INDEX NAME)



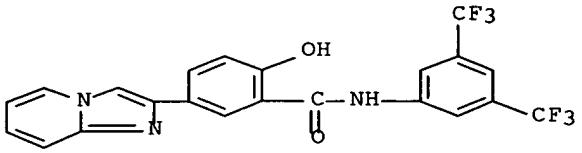
RN 439144-38-4 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(3-thienyl)- (CA INDEX NAME)



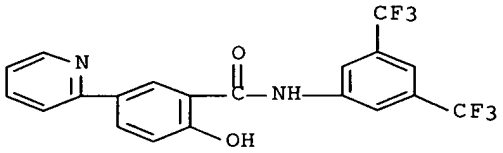
RN 439144-39-5 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-methyl-4-thiazolyl)- (CA INDEX NAME)



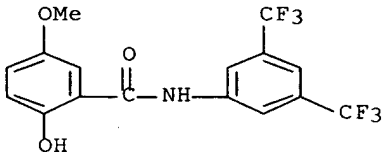
RN 439144-40-8 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-imidazo[1,2-a]pyridin-2-yl- (CA INDEX NAME)



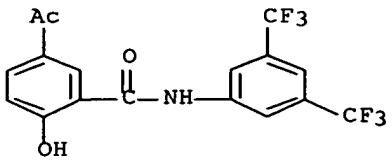
RN 439144-41-9 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-pyridinyl)- (CA INDEX NAME)



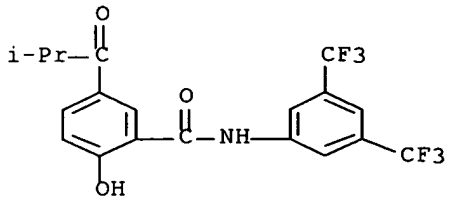
RN 439144-42-0 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-methoxy- (CA INDEX NAME)



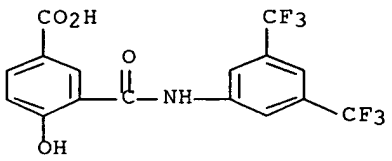
RN 439144-43-1 HCAPLUS
CN Benzamide, 5-acetyl-N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



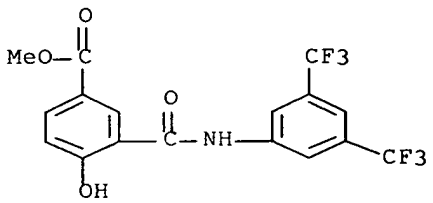
RN 439144-44-2 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(2-methyl-1-oxopropyl)- (CA INDEX NAME)



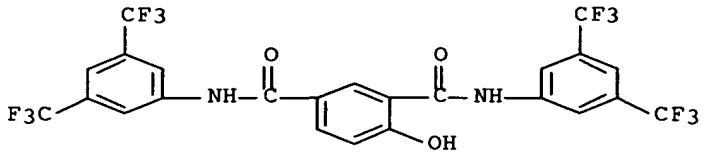
RN 439144-45-3 HCAPLUS
CN Benzoic acid, 3-[[[3,5-bis(trifluoromethyl)phenyl]amino]carbonyl]-4-hydroxy- (CA INDEX NAME)



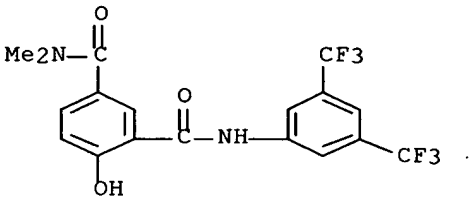
RN 439144-46-4 HCAPLUS
CN Benzoic acid, 3-[[[3,5-bis(trifluoromethyl)phenyl]amino]carbonyl]-4-hydroxy-, methyl ester (CA INDEX NAME)



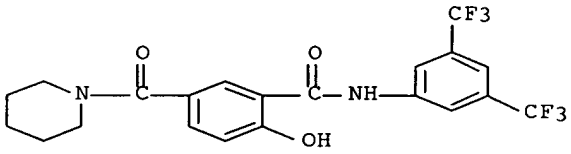
RN 439144-47-5 HCAPLUS
CN 1,3-Benzenedicarboxamide, N,N'-bis[3,5-bis(trifluoromethyl)phenyl]-4-hydroxy- (9CI) (CA INDEX NAME)



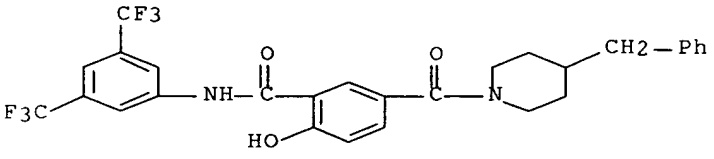
RN 439144-48-6 HCAPLUS
CN 1,3-Benzenedicarboxamide, N3-[3,5-bis(trifluoromethyl)phenyl]-4-hydroxy-N1,N1-dimethyl- (CA INDEX NAME)



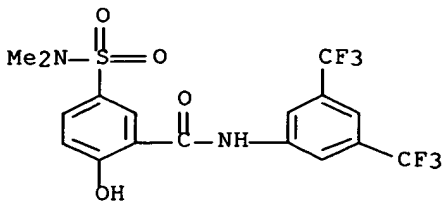
RN 439144-49-7 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(1-piperidinylcarbonyl)- (CA INDEX NAME)



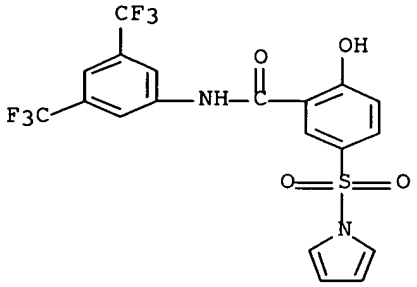
RN 439144-50-0 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]- (CA INDEX NAME)



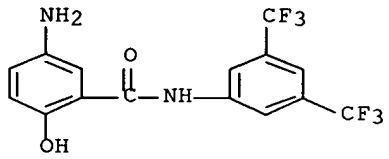
RN 439144-51-1 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-[(dimethylamino)sulfonyl]-2-hydroxy- (CA INDEX NAME)



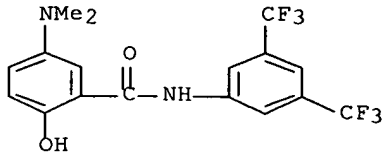
RN 439144-52-2 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-(1H-pyrrol-1-ylsulfonyl)- (CA INDEX NAME)



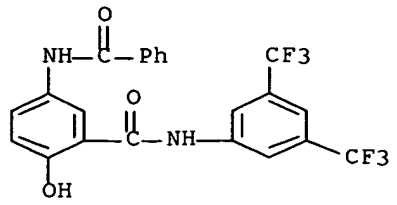
RN 439144-53-3 HCAPLUS
CN Benzamide, 5-amino-N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



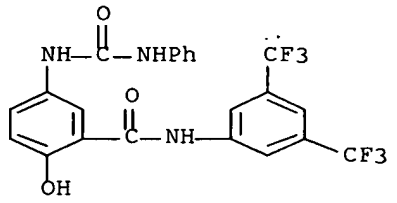
RN 439144-54-4 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-5-(dimethylamino)-2-hydroxy- (CA INDEX NAME)



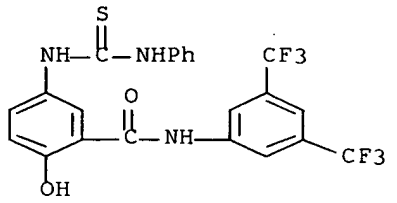
RN 439144-55-5 HCAPLUS
CN Benzamide, 5-(benzoylamino)-N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



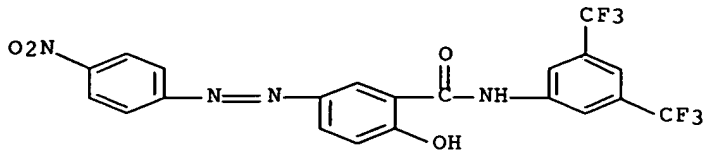
RN 439144-56-6 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[[(phenylamino)carbonyl]amino]- (CA INDEX NAME)



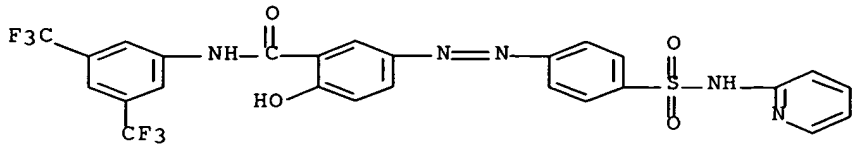
RN 439144-57-7 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[[(phenylamino)thioxomethyl]amino]- (CA INDEX NAME)



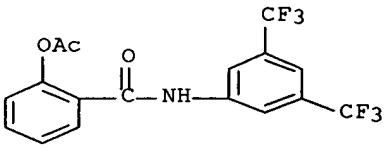
RN 439144-58-8 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[(4-nitrophenyl)azo]- (9CI) (CA INDEX NAME)



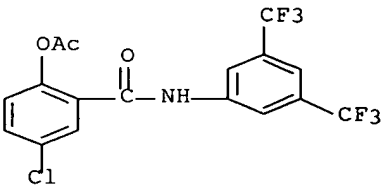
RN 439144-59-9 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl]phenyl]azo]- (9CI) (CA INDEX NAME)



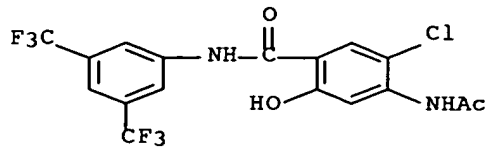
RN 439144-60-2 HCAPLUS
CN Benzamide, 2-(acetyloxy)-N-[3,5-bis(trifluoromethyl)phenyl]- (CA INDEX NAME)



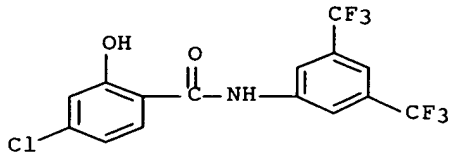
RN 439144-61-3 HCAPLUS
CN Benzamide, 2-(acetyloxy)-N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro- (CA INDEX NAME)



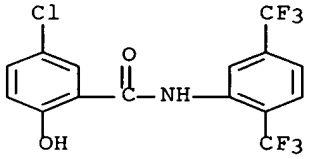
RN 439144-62-4 HCAPLUS
CN Benzamide, 4-(acetylamino)-N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxy- (CA INDEX NAME)



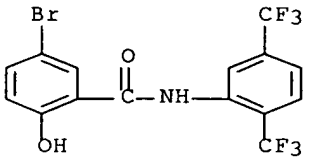
RN 439144-63-5 HCAPLUS
CN Benzamide, N-[3,5-bis(trifluoromethyl)phenyl]-4-chloro-2-hydroxy- (CA INDEX NAME)



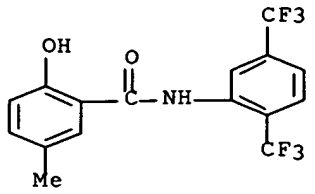
RN 439144-65-7 HCAPLUS
CN Benzamide, N-[2,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxy- (CA INDEX NAME)



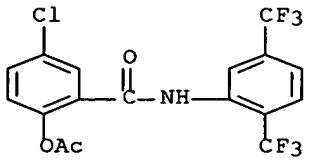
RN 439144-66-8 HCAPLUS
CN Benzamide, N-[2,5-bis(trifluoromethyl)phenyl]-5-bromo-2-hydroxy- (CA INDEX NAME)



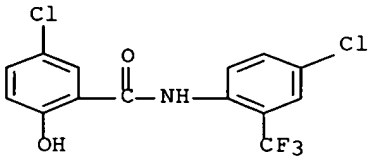
RN 439144-67-9 HCAPLUS
CN Benzamide, N-[2,5-bis(trifluoromethyl)phenyl]-2-hydroxy-5-methyl- (CA INDEX NAME)



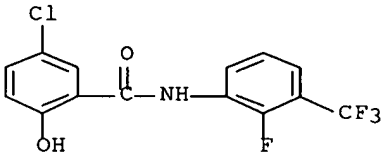
RN 439144-68-0 HCAPLUS
CN Benzamide, 2-(acetyloxy)-N-[2,5-bis(trifluoromethyl)phenyl]-5-chloro- (CA INDEX NAME)



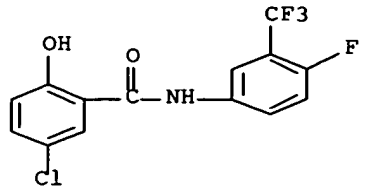
RN 439144-70-4 HCAPLUS
CN Benzamide, 5-chloro-N-[4-chloro-2-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



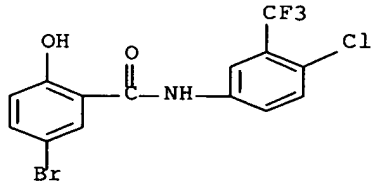
RN 439144-72-6 HCAPLUS
CN Benzamide, 5-chloro-N-[2-fluoro-3-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



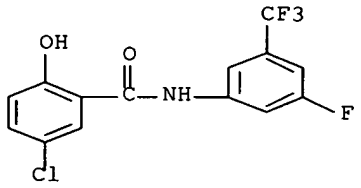
RN 439144-73-7 HCAPLUS
CN Benzamide, 5-chloro-N-[4-fluoro-3-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



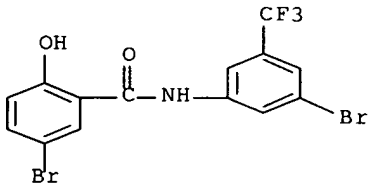
RN 439144-74-8 HCAPLUS
CN Benzamide, 5-bromo-N-[4-chloro-3-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



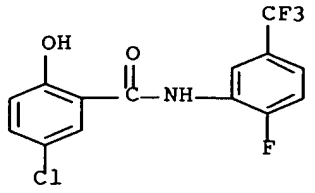
RN 439144-75-9 HCAPLUS
CN Benzamide, 5-chloro-N-[3-fluoro-5-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



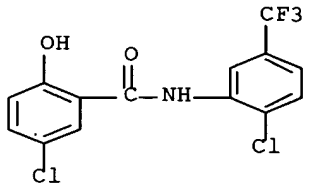
RN 439144-76-0 HCAPLUS
CN Benzamide, 5-bromo-N-[3-bromo-5-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



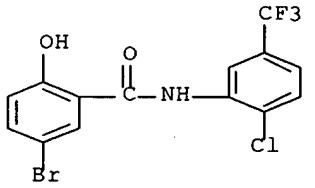
RN 439144-77-1 HCAPLUS
CN Benzamide, 5-chloro-N-[2-fluoro-5-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



RN 439144-78-2 HCAPLUS
CN Benzamide, 5-chloro-N-[2-chloro-5-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



RN 439144-79-3 HCAPLUS
CN Benzamide, 5-bromo-N-[2-chloro-5-(trifluoromethyl)phenyl]-2-hydroxy- (CA INDEX NAME)



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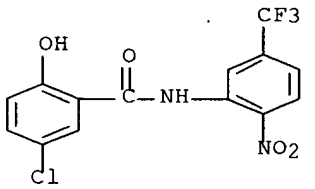

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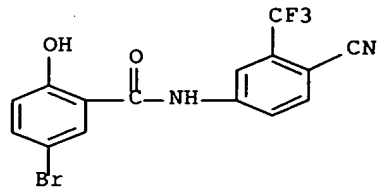

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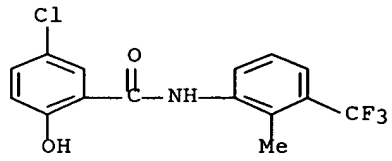

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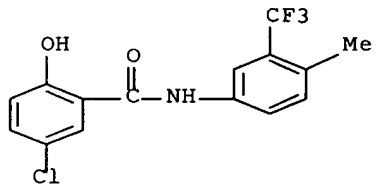

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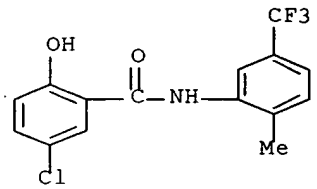

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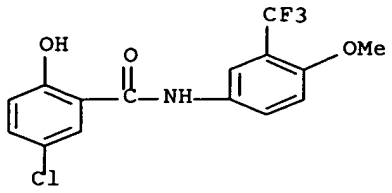


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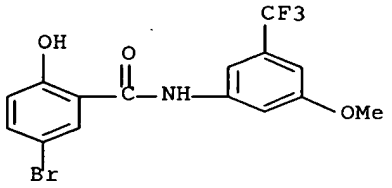


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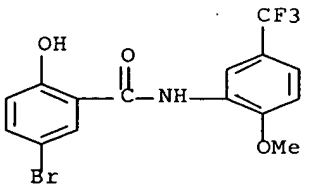


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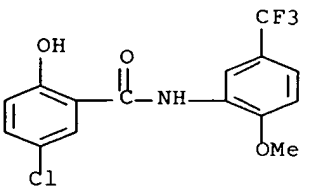

# Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer

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NF-κB comprises a family of inducible transcription factors that serve as important regulators of the host immune and inflammatory response. In addition, NF-κB is also involved in protecting cells from undergoing apoptosis in response to DNA damage or cytokine treatment. Stimulation of the NF-κB pathway is mediated by diverse signal transduction cascades. These signals activate the IκB kinases, IKKα and IKKβ, which phosphorylate inhibitory proteins known as IκB to result in their ubiquitination and degradation by the proteasome. The degradation of IκB results in the translocation of NF-κB from the cytoplasm to the nucleus where it activates the expression of specific cellular genes. As we better understand the regulation of the NF-κB pathway, the potential for inhibiting this pathway has received attention. Agents that inhibit this pathway, such as glucocorticoids and aspirin, can reduce the inflammatory response, while other agents such as dominant negative IκB proteins potentiate the effects of chemotherapy and radiation therapy in the treatment of cancer. Here, we discuss cellular genes and disease states associated with activation of the NF-κB pathway and consider therapeutic strategies to prevent the prolonged activation of the NF-κB pathway.

## NF-κB activation of cellular genes involved in the immune and inflammatory response

NF-κB regulates host inflammatory and immune responses (1–4) and cellular growth properties (5) by increasing the expression of specific cellular genes. These include genes encoding at least 27 different cytokines and chemokines, receptors involved in immune recognition such as members of the MHC, proteins involved in antigen presentation, and receptors required for neutrophil adhesion and migration (2). Cytokines that are stimulated by NF-κB, such as IL-1β and TNF-α, can also directly activate the NF-κB pathway, thus establishing a positive autoregulatory loop that can amplify the inflammatory response and increase the duration of chronic inflammation.

NF-κB also stimulates the expression of enzymes whose products contribute to the pathogenesis of the inflammatory process, including the inducible form of nitric oxide synthase (iNOS), which generates nitric oxide (NO), and the inducible cyclooxygenase (COX-2), which generates prostanoids (2). The NF-κB pathway is likewise important in the control of the immune response. It modulates B-lymphocyte survival, mitogen-dependent cell proliferation, and isotype switching, which lead to the differentiation of B lymphocytes into plasma cells (3). In addition, NF-κB regulates IL-2 production, which increases the proliferation and differentiation of T lymphocytes (2, 3). Thus, activation of NF-κB leads to the induction of multiple genes that regulate the immune and the inflammatory response.

## NF-κB regulation of cellular apoptosis and proliferation

In addition to activating the expression of genes involved in the control of the immune and inflammatory response, the NF-κB pathway is also a key mediator of genes involved in the control of the cellular proliferation and apoptosis (5). Antiapoptotic genes that are directly activated by NF-κB include the cellular inhibitors of apoptosis (c-IAP1, c-IAP2, and IXAP), the TNF receptor–associated factors (TRAF1 and TRAF2), the Bcl-2 homologue A1/Bfl-1, and IEX-IL (6, 7).

One of the best-studied pathways that activates apoptosis is induced following treatment of cells with TNF-α. TNF-α treatment increases the expression of TRAF1, TRAF2, c-IAP1, and c-IAP2 (6). The overexpression of these proteins can protect RelA-deficient cells, which are highly sensitive to TNF-α–induced apoptosis, from cell death. These antiapoptotic proteins block the activation of caspase-8, an initiator protease, involved at an early step in stimulating the apoptotic pathway (6).

Members of the Bcl-2 family may be antiapoptotic, as is the case with Bcl-2, Bcl-xL, and A1/Bfl-1, or proapoptotic, as with Bad, Bax, and Bcl-xS. NF-κB directly induces expression of A1/Bfl-1 by binding to specific sites in its promoter (8). The constitutive expression of A1/Bfl-1 inhibits antigen receptor–induced apoptosis in B lymphocytes derived from c-Rel–deficient mice, suggesting that NF-κB activation of this protein plays an important role in the B lymphocyte survival follow-

ing lymphocyte activation (8). The chemotherapeutic agent etoposide also increases NF-κB levels and thereby induces A1/Bfl-1, which prevents cytochrome *c* release from mitochondria and activation of caspase-3 (9). By increasing the expression of antiapoptotic cellular proteins, NF-κB activation can thus reduce apoptosis in response to treatment with different chemotherapeutic agents.

NF-κB also acts in the control of the cell cycle, which is a critical element in determining the degree of cellular apoptosis and proliferation. NF-κB activates the expression of cyclin D1, a positive regulator of G1-to-S-phase progression, by direct binding to multiple sites in its promoter (10). Inhibition of NF-κB activation can reduce cyclin D1 activity and subsequent phosphorylation of the retinoblastoma protein to result in delayed cell cycle progression. This impaired cell cycle progression can be rescued by ectopic expression of cyclin D1 (11). Thus, the suppression of apoptosis induced by NF-κB involves the regulation of multiple genes involved in different aspects of growth control.

## Role of NF-κB in pathogenesis of human disease

Activation of the NF-κB pathway is involved in the pathogenesis of chronic inflammatory diseases, such as asthma, rheumatoid arthritis (see Tak and Firestein, this Perspective series, ref. 12), and inflammatory bowel disease. In addition, altered NF-κB regulation may be involved in other diseases such as atherosclerosis (see Collins and Cybulsky, this series, ref. 13) and Alzheimer's disease (see Mattson and Camandola, this series, ref. 14), in which the inflammatory response is at least partially involved. Finally, abnormalities in the NF-κB pathway are also frequently seen in a variety of human cancers.

Several lines of evidence suggest that NF-κB activation of cytokine genes is an important contributor to the pathogenesis of asthma, which is characterized by the infiltration of inflammatory cells and the dysregulation of many cytokines and chemokines in the lung (15). Likewise, activation of the NF-κB pathway also likely plays a role in the pathogenesis of rheumatoid arthritis. Cytokines, such as TNF-α, that activate NF-κB are elevated in the synovial fluid of patients with rheumatoid arthritis and contribute to the chronic inflammatory changes and synovial hyperplasia seen in the joints of these patients (16). The administration of antibodies directed against TNF-α or a truncated TNF-α receptor that binds to TNF-α can markedly improve the symptoms of patients with rheumatoid arthritis.

Increases in the production of proinflammatory cytokines by both lymphocytes and macrophages has also been implicated in the pathogenesis of inflammatory bowel diseases, including Crohn's disease and ulcerative colitis (17). NF-κB activation is seen in mucosal biopsy specimens from patients with active Crohn's disease and ulcerative colitis. Treatment of patients with inflammatory bowel diseases with steroids decreases NF-κB activity in biopsy specimens and reduces clinical symptoms. These results suggest that stimulation of the NF-κB pathway may be involved in the enhanced inflammatory response associated with these diseases.

Atherosclerosis is triggered by numerous insults to the endothelium and smooth muscle of the damaged vessel wall (18). A large number of growth factors, cytokines, and chemokines released from endothelial cells, smooth muscle, macrophages, and lymphocytes are involved in this chronic inflammatory and fibroproliferative process (18). NF-κB regulation of genes involved in the inflammatory response and in the control of cellular proliferation likely plays an important role in the initiation and progression of atherosclerosis.

Finally, abnormalities in the regulation of the NF-κB pathway may be involved in the pathogenesis of Alzheimer's disease. For example, NF-κB immunoreactivity is found predominantly in and around early neuritic plaque types in Alzheimer's disease, whereas mature plaque types show vastly reduced NF-κB activity (19). Thus, NF-κB activation may be involved in the initiation of neuritic plaques and neuronal apoptosis during the early phases of Alzheimer's disease. These data suggest that activation of the NF-κB pathway may play a role in a number of diseases that have an inflammatory component involved in their pathogenesis.

In addition to a role in the pathogenesis of diseases characterized by increases in the host immune and inflammatory response, constitutive activation of the NF-κB pathway has also been implicated in the pathogenesis of some human cancers. Abnormalities in the regulation of the NF-κB pathway are frequently seen in a variety of human malignancies including leukemias, lymphomas, and solid tumors (20). These abnormalities result in constitutively high levels of NF-κB in the nucleus of a variety of tumors including breast, ovarian, prostate, and colon cancers. The majority of these changes are likely due to alterations in regulatory proteins that activate signaling pathways that lead to activation of the NF-κB pathway. However, mutations that inactivate the IκB proteins in addition to amplification and rearrangements of genes encoding NF-κB family members can result in the enhanced nuclear levels of NF-κB seen in some tumors.

## Potential targets for inhibiting the NF-κB pathway

Activation of the NF-κB pathway requires a number of discrete steps. It is important to review this pathway in order to better understand how different agents can prevent the activation of this pathway. The NF-κB proteins comprise a family of proteins that share a 300-amino acid domain that is designated the Rel homology domain (1, 4). The Rel homology domain mediates the DNA binding, dimerization, and nuclear transport of the NF-κB proteins. In addition to the Rel

homology domain, the NF-κB family members c-Rel, RelB, and p65 also contain a transactivation domain. The NF-κB family members p50 and p52, which are derived from the inactive precursors p105 and p100, respectively, possess DNA binding and dimerization properties but not strong transactivation domains. It is the differential expression of these proteins, their ability to heterodimerize with different family members, and the interaction of these proteins with different components of the transcription apparatus that contribute to the diverse effects of activating the NF-κB pathway.

In unstimulated cells, NF-κB proteins are localized in the cytoplasm, associated with a family of inhibitor proteins known as IκB (IκBα, IκBβ, IκBε) (1, 4). The IκB proteins contain several distinct domains, including ankyrin repeats that are critical for IκB interactions with NF-κB, an $NH_2$-terminal regulatory domain that is a target for the inducible phosphorylation and subsequent ubiquitination of IκB, and a COOH-terminal PEST domain that is important in regulating IκB turnover. The IκB proteins bind to NF-κB and block their nuclear localization signal. A variety of stimuli including cytokines such as TNF-α and IL-1, phorbol esters, LPS, viral infection, the human T-cell leukemia virus type 1–transforming protein Tax, ultraviolet radiation, and free radicals result in the degradation of IκB and the nuclear translocation of NF-κB (2).

The phosphorylation of the IκB proteins is a key step involved in the regulation of Rel/NF-κB complexes. The phosphorylation of the IκB proteins is mediated by IκB kinases (IKKs) (21), whose activity is strongly induced by activators of the NF-κB pathway (1, 4). IKK activity is present in a high-molecular-weight complex containing at least two kinase subunits, IKKα and IKKβ, and the associated modulatory protein, IKKγ or NEMO (21). The IKKs have 52% amino acid identity and a similar structural organization, which includes kinase, leucine zipper, and helix-loop-helix domains. These kinases are able to form both homo- and heterodimers. Biochemical analysis and gene disruption studies of the IKK genes in mice indicate that IKKβ is the critical kinase involved in activating the NF-κB pathway, while IKKα likely plays an accessory role (21). However, both IKKα and IKKβ are essential genes for mouse viability. The activated IKK complex phosphorylates the IκB proteins on two closely spaced serine residues in the amino terminus of these proteins (1, 4). Phosphorylation of IκB leads to its ubiquitination on two amino-terminal lysine residues by the E3 ubiquitin ligase complex, thus targeting it for degradation by the 26S proteasome (21). Freed of their association with the IκB subunits, the NF-κB proteins translocate to the nucleus, where they bind to specific elements in the promoter regions of target genes to activate gene expression.

Activation of the NF-κB pathway can result from stimulation by a variety of different signal transduction pathways. Although IKK is a key regulator of the NF-κB pathway, ubiquitination of IκB and its subsequent degradation by the proteasome are also required for NF-κB activation. Furthermore, the differential nuclear translocation of members of the NF-κB family and the specific phosphorylation of these proteins are also involved in the ability of the NF-κB proteins to activate gene expression. Given the diverse processes involved in activating the NF-κB pathway, it is not surprising that a number of different inhibitors can prevent activation of this pathway. In the following sections, we discuss the mechanisms by which these inhibitors alter the NF-κB pathway in inflammatory states and cancer.

### Inhibition of the NF-κB pathway using degradation-resistant IκB proteins

The first evidence that the NF-κB pathway could be specifically inhibited came from studies of IκBα mutants (1, 4). Signal-induced phosphorylation and degradation of cytoplasmic IκBα is required for NF-κB pathway activation. However, an IκBα protein with mutations at serine residues 32 and 36 is not subject to phosphorylation by IKK and is not degraded by the proteasome. This IκBα mutant or super-repressor has a dominant negative phenotype because it sequesters NF-κB in the cytoplasm and thus prevents the induction of specific NF-κB target genes.

Blocking the NF-κB pathway by the IκBα super-repressor enhances the sensitivity of cells to apoptosis-inducing stimuli. For example, TNF-α treatment of cells induces the NF-κB pathway and results in cellular apoptosis (22, 23). Since NF-κB protects cells from undergoing apoptosis, blocking this pathway enhances apoptosis. The expression of the IκBα super-repressor enhances sensitivity to TNF-α–induced apoptosis in Jurkat cells, which are otherwise relatively resistant to apoptosis (22, 23). The migration of phosphatidylserine from the inner to the outer leaflet of plasma membrane, which is an early event in apoptosis, is also markedly increased in TNF-α–treated Jurkat cells expressing the IκBα super-repressor (23). The expression of this IκBα protein in the human fibrosarcoma cells also enhances their sensitivity to apoptotic killing by ionizing radiation or the chemotherapeutic agent daunorubicin, each of which are able to activate the NF-κB pathway (22). In contrast, the IκBα super-repressor does not have any effect on preventing apoptosis induced by the kinase inhibitor staurosporine, which induces cell death in an NF-κB–independent manner. These results indicate that the IκBα super-repressor can enhance cell killing by blocking the NF-κB pathway.

The adenoviral delivery of the IκBα super-repressor to chemoresistant tumors in mice sensitizes these cells to undergo apoptosis in response to treatment with either TNF-α or the chemotherapeutic agent CPT-11, resulting in tumor regression (ref. 24; see also Baldwin, this Perspective series, ref. 25). The IκBα super-repressor also

suppresses constitutive and TNF-α–induced NF-κB activity in human head and neck carcinoma cells in tissue culture and reduces the growth of such tumors in SCID mice (24). These results suggest that the IκBα super-repressor inhibits the expression of NF-κB–dependent genes, which can enhance the growth of squamous cell carcinomas. Thus, NF-κB has an important role in the regulation of cellular proliferation, and inhibition of the NF-κB pathway may enhance the efficacy of cancer chemotherapy.

### Diverse mechanisms involved in glucocorticoid-mediated repression of the NF-κB pathway

Glucocorticoids, such as dexamethasone and prednisone, are widely used for their anti-inflammatory and immunosuppressive properties. These agents interact with the steroid receptor to downregulate the expression of specific genes that regulate the inflammatory process. There are several proposed mechanisms to explain the inhibitory effects of glucocorticoids on the NF-κB pathway.

The first mechanism is consistent with a role for glucocorticoids in inducing expression of IκBα to enhance the cytosolic retention of NF-κB (26, 27). Dexamethasone induces the synthesis of IκBα mRNA in glucocorticoid receptor–expressing Jurkat cells (26) and in monocytic cells (27), increasing the level of IκBα and resulting in the cytoplasmic retention of p65. The majority of newly synthesized IκBα induced by dexamethasone is associated with p65 in pre-existing NF-κB complexes (27). Glucocorticoid-mediated inhibition of NF-κB DNA binding is blocked by the addition of cycloheximide, an inhibitor of protein synthesis. Taken together, these results demonstrate that the rapid degradation of IκBα protein seen in response to either TNF-α or phorbol ester treatment of cells can be compensated by dexamethasone-induced synthesis of IκBα. NF-κB is thus maintained in an inactive cytoplasmic complex so that the expression of genes involved in the pathogenesis of the immune response is reduced.

However, other mechanisms are also likely involved in glucocorticoid-mediated repression of the NF-κB pathway. For example, dexamethasone can repress IL-6 expression and p65-dependent transactivation in murine endothelial fibroblasts without changing IκB protein levels or NF-κB DNA-binding activity (28). Similarly, in primary endothelial cells, dexamethasone reduces NF-κB–mediated transcriptional activity without altering IκB protein levels or the nuclear translocation of NF-κB. These results indicate that in certain cell types the downmodulation of NF-κB–directed gene expression by glucocorticoids is due to other mechanisms. For example, direct protein-protein interactions between the activated glucocorticoid receptor and NF-κB can also prevent activation of this pathway (28, 29). Protein crosslinking and coimmunoprecipitation studies demonstrate a physical association between the activated glucocorticoid receptor and the p65 subunit of NF-κB.

Competition between NF-κB and the glucocorticoid receptor for limiting amounts of the coactivators CREB-binding protein (CBP) and steroid receptor coactivator-1 (SRC-1) has also been proposed to explain glucocorticoid-mediated inhibition of NF-κB (30). These coactivators bind to both p65 and the glucocorticoid receptor and are critical for the transactivation properties of both of these proteins. Cotransfection assays demonstrate that the expression of increasing amounts of coactivators counteracts glucocorticoid-mediated repression of the NF-κB pathway. These results implicate coactivators in the antagonistic interaction between the glucocorticoid receptor and p65. However, a recent study demonstrates that glucocorticoid-mediated repression of NF-κB activity occurs irrespective of coactivator levels (31), suggesting that glucocorticoid repression of p65 transactivation is specifically determined by the context of the TATA box relative to the κB binding sites in different promoters. Thus, it is possible that the glucocorticoid receptor directly disrupts p65 interactions with the basal transcription machinery, by direct interactions either with p65 or with components of the basal transcription complex.

### Nonsteroidal anti-inflammatory drugs and IKK activity

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory states. In addition, these agents induce the regression of adenomatous polyps of the colon and prevent the development of colon cancer. The most commonly accepted theory to account for the inhibitory effects of these agents on the inflammatory response and the prevention of colon cancer holds that NSAIDs inhibit COX activity to prevent prostaglandin synthesis (32). However, other reports suggest that additional mechanisms are involved in the actions of these agents (33–35).

Aspirin and sodium salicylate are examples of anti-inflammatory agents for which the molecular target is, at least in part, NF-κB. At concentrations measured in the serum of patients treated with these agents for chronic inflammatory conditions, both aspirin and salicylate inhibit activation of the NF-κB pathway (33–35). These agents suppress TNF-α–induced mRNA synthesis of adhesion molecules and surface expression of VCAM-1 and ICAM-1 in endothelial cells (33). This inhibition of the NF-κB pathway in endothelial cells prevents transendothelial migration of neutrophils, suggesting that the clinical importance of high-dose salicylates as anti-inflammatory agents is at least partially due to blocking NF-κB activation to inhibit leukocyte recruitment (33).

Recently, Yin et al. found that the inhibitory effects of aspirin and sodium salicylate result from the specific

inhibition of ATP-binding to IKKβ (34). Thus, IKKβ-dependent phosphorylation of IκBα is markedly reduced, preventing its degradation by the proteasome and activation of the NF-κB pathway. In contrast, concentrations of indomethacin that inhibit COX activity and result in potent anti-inflammatory responses do not prevent activation of the NF-κB pathway (33, 34). Hence, the effects of aspirin and sodium salicylate on inhibiting the NF-κB pathway appear to be independent of their ability to block COXs.

Sulfasalazine is an anti-inflammatory agent that is used in the management of inflammatory bowel disease and rheumatoid arthritis. It combines a nonsteroidal anti-inflammatory moiety (5-aminosalicylic acid; 5-ASA) and an antibacterial moiety (sulfapyridine). After oral administration, about 70% of sulfasalazine is degraded by colonic bacteria to 5-ASA and sulfapyridine. Treatment of colonic epithelial cells with sulfasalazine, but not 5-ASA or sulfapyridine, inhibits NF-κB activation induced by treatment with either TNF-α, LPS, or phorbol ester (36). The inhibition of the NF-κB pathway by sulfasalazine is associated with suppression of IκBα phosphorylation and its subsequent degradation. Although the exact role of sulfapyridine in inhibiting NF-κB remains unclear, sulfasalazine appears to owe part of its therapeutic effect to 5-ASA–mediated suppression of NF-κB activation. Interestingly, a related aminosalicylate derivative with anti-inflammatory properties, mesalamine, prevents IL-1–mediated stimulation of p65 phosphorylation without inhibiting IκBα degradation (37). Thus, nonsteroidal anti-inflammatory agents may inhibit the NF-κB pathway at multiple steps.

Sulindac is a nonsteroidal anti-inflammatory agent that is structurally related to indomethacin. In the colon, sulindac is converted by bacteria to the metabolites sulindac sulfide, which blocks prostaglandin synthesis by nonselective inhibition of COX-1 and COX-2, and sulindac sulfone, which has no such inhibitory effect. Nevertheless, sulindac and both of these metabolites can inhibit activation of the NF-κB pathway by inhibiting IKK activity (35). In addition, sulindac and aspirin induce apoptosis in HCT-15 cells, a colon carcinoma cell line that is defective in the generation of prostaglandins (35). These results suggest that inhibition of the NF-κB pathway may be involved in the anti-inflammatory as well as the growth inhibitory properties of certain NSAIDs.

### Inhibition of the NF-κB pathway by immunosuppressive agents

Cyclosporin A (CsA) and tacrolimus (FK-506) are immunosuppressive agents used in organ transplantation to prevent graft-versus-host disease. These agents, in a complex with the cellular protein cyclophilin, inhibit the activity of calcineurin, a calcium- and calmodulin-dependent serine/threonine phosphatase, to result in the inhibition of cell activation. Calcineurin is required for activation of the transcription factor NF-AT, which binds to the *IL2* promoter and is critical for regulating IL-2 expression in T lymphocytes. In addition, calcineurin can activate the NF-κB pathway (38). In Jurkat cells, transfection of an expression vector containing a $Ca^{2+}$-independent calcineurin protein results in increased DNA binding and transactivation by NF-κB. Hence, FK-506 and CsA inhibition of calcineurin activity can prevent NF-κB activation under specific conditions.

FK-506 and CsA act by distinct mechanisms to inhibit the NF-κB pathway (38–41). CsA serves as a noncompetitive inhibitor of the chymotrypsin-like activity of the 20S proteasome and thus prevents IκBα degradation and activation of the NF-κB pathway. This agent inhibits proteasome activity in vitro and suppresses LPS-induced IκB degradation in murine macrophages by stabilizing the ubiquitinated forms of IκBα (38). This finding suggests that a target of CsA in inhibiting the NF-κB pathway is the protease activity of the proteasome rather than kinases or ubiquitin ligases that regulate the signal-induced phosphorylation and ubiquitination of IκB, respectively. Similar results are seen in Jurkat cells, as well as human and mouse primary T lymphocytes, where CsA interferes with the degradation of IκBα following phorbol-ester and ionomycin stimulation without altering IκBα phosphorylation (39). The proteolytic processing of the NF-κB precursor p105, which also requires the 26S proteasome complex, is not affected by CsA treatment (40).

FK-506 appears to act by a different mechanism to inhibit the NF-κB pathway (41), specifically blocking translocation of c-Rel from the cytoplasm to the nucleus. FK-506 blocks both antigen receptor–induced and phorbol ester and ionomycin–induced c-Rel nuclear translocation in both B and T cells; neither RelB induction nor p50 expression is altered by FK-506 treatment (41). Furthermore, FK-506 suppresses c-Rel–induced transactivation of the gene for the IL-2 receptor α-chain. Coexpression of a constitutively active calcineurin activates expression from this gene, suggesting that a calcineurin-dependent pathway is involved in c-Rel activation. Thus, a portion of the immunosuppressive effects of FK-506 may result from inhibition of c-Rel translocation to result in decreased expression of both IL-2 and its receptor.

### Downregulation of the NF-κB pathway by cyclopentenone prostaglandins

NF-κB regulates the expression of a variety of genes involved in the immune and inflammatory responses, including COX-2. COX-1 is constitutively expressed in most tissues, whereas COX-2 is an inducible enzyme whose expression is enhanced in response to inflammatory stimuli. COX-2 directs the synthesis of anti-inflammatory cyclopentenone prostaglandins (cyPGs), which are involved in the resolution phase of

inflammation. CyPGs act as intracellular regulators of inflammatory and immune responses as well as cellular proliferation.

Two roles of cyPGs in regulation of the NF-κB pathway have been proposed (42, 43). First, cyPGs have been suggested to exert their anti-inflammatory activity through the activation of PPARγ, a member of the nuclear receptor superfamily. 15-deoxy-$\Delta^{12,14}$ prostaglandin $J_2$ (15dPGJ$_2$; bioactive prostaglandin $D_2$ metabolite) binds and activates PPARγ, and in activated macrophages, 15dPGJ$_2$ inhibits the expression of gelatinase B and NOS and other NF-κB–regulated genes in a PPARγ-dependent manner (42).

Other groups have demonstrated that cyPGs themselves can directly inhibit NF-κB activity (43). The cyPG metabolite $PGA_1$ inhibits TNF-α–induced phosphorylation of IκBα, NF-κB DNA binding, and NF-κB transactivation in Jurkat lymphoma cells. A recent study indicates that $PGA_1$ and 15dPGJ$_2$ directly inhibit the IKKβ activity (43). The inhibition of IKKβ activity by cyPGs is due to modification of a cysteine residue in the activation loop of IKKβ. As NF-κB regulates COX-2 synthesis, the inhibition of NF-κB transactivation by cyPGs may be part of a negative feedback loop that contributes to resolution of inflammation.

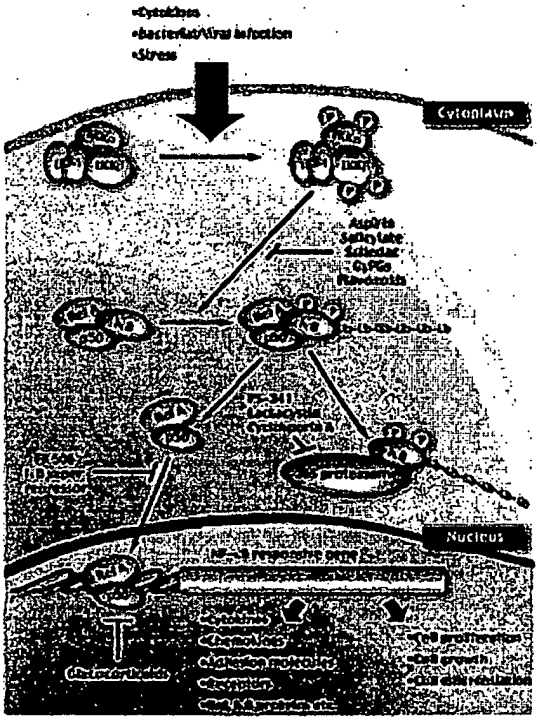


**Figure 1**
Inhibition of the NF-κB pathway. A schematic illustrating the steps involved in the activation of the NF-κB pathway. Numerous drugs, natural products, and normal or recombinant proteins can act at several of these steps to interfere with NF-κB activation.

### Inhibition of proteasome function prevents IκB degradation

Signal-induced phosphorylation and ubiquitination of IκB and its degradation by the 26S proteasome precede NF-κB nuclear translocation. Inhibitors of proteasome function reduce the degradation of IκB to prevent activation of the NF-κB pathway (1, 4). A variety of peptide aldehydes, including MG101, MG132, and MG115, make up one class of agents that inhibit the protease activity of the proteasome. Proteasome inhibitors of another class, including lactacystin, block protein degradation activity by acylating a threonine residue in one of the key proteasome subunits. Finally, a group of boronic acid peptides, including PS-341, are extremely potent inhibitors of proteasome function (44). Recently, PS-341 has shown promise as an adjunct to cancer chemotherapy by inhibiting activation of the NF-κB pathway. It is also possible that inhibitors of the ubiquitin ligase that mediates IκB ubiquitination may be a useful target in preventing proteasome degradation of IκB. Thus, a variety of potential inhibitors of proteasome function may have a role interrupting the NF-κB pathway.

### Natural products that inhibit the NF-κB pathway

Flavonoids are naturally occurring phenolic compounds, found in plants, that exhibit a variety of biological activities, including suppression of inflammation, cancer chemoprevention, and protection from vascular disease. Several reports suggest that the properties of the flavonoids quercetin, resveratrol, and myricetin may be mediated through downregulation of the NF-κB pathway (45, 46). For example, resveratrol, which is found in red wine, can inhibit NF-κB activity and induce apoptosis in transformed cells, which may contribute to the ability of red wine to reduce mortality from coronary heart diseases and certain cancers (46). Resveratrol has strong inhibitory effects on iNOS expression and NO generation in activated macrophages (45). Treatment of macrophages with this compound blocks LPS-induced phosphorylation and degradation of IκBα to decrease NF-κB DNA binding activity, suggesting that its anti-inflammatory effects may be due at least in part to the inhibition of NF-κB–dependent NO synthesis (45). The inhibitory effects of resveratrol and the flavonoid myricetin on activation of the NF-κB pathway correlate with their ability to reduce IKK activity (46). Thus several of the biological activities of flavonoids may be mediated by their inhibition of the NF-κB pathway.

## Therapeutic implications and perspective

A better understanding of the regulation of the NF-κB pathway may provide opportunities for the development of new treatments to inhibit prolonged activation of this pathway. As shown in Figure 1, NF-κB is an obvious target for new types of treatment to block the inflammatory response in instances where this process becomes chronic or dysregulated. A variety of widely used anti-inflammatory agents inhibit the NF-κB pathway, at least in part, as one of their targets. One concern about inhibiting several of these components of the NF-κB pathway is the specificity of such drugs. For example, the proteasome which is responsible for IκB degradation has many other important functions. Thus, inhibition of proteasome activity could potentially cause severe side effects. It may also not be feasible to block the NF-κB pathway for prolonged periods, since NF-κB plays an important role in the maintenance of host defense responses. The prolonged expression in the liver of a degradation-resistant IκB super-repressor protein in transgenic mice indicates that inhibition of NF-κB activity can occur without liver dysfunction, although the animals were more susceptible to bacterial infection (47). However, short term treatment with specific inhibitors of IKK activity might reduce such potential side effects. It is possible that specific inhibitors of IKK activity may provide a new class of anti-inflammatory and anticancer agents or of adjunct therapeutics to enhance the efficacy of other cancer therapies (see Baldwin, this Perspective series, ref. 25).

Although the maintenance of appropriate levels of NF-κB activity is a critical factor in achieving normal cellular proliferation, constitutive NF-κB activation is likely involved in the enhanced growth properties seen in a variety of cancers. The potential applications of inhibition of the NF-κB pathway in cancer chemotherapy are in their early stages. However, such approaches offer the promise of enhancing the efficacy of cancer chemotherapy and reducing abnormal cytokine production, which may contribute to the growth of certain tumors.

## Acknowledgments

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# 2-Chloro-4-(trifluoromethyl)pyrimidine-5-*N*-(3′,5′-bis(trifluoromethyl)phenyl)-carboxamide: A Potent Inhibitor of NF-κB- and AP-1-Mediated Gene Expression Identified Using Solution-Phase Combinatorial Chemistry

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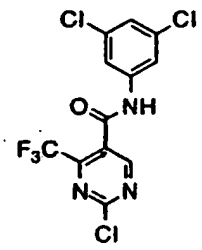
Described is the identification of a novel series of compounds that blocks the activation of two key transcription factors, AP-1 and NF-κB. These transcription factors regulate the expression of several critical proinflammatory proteins and cytokines and represent attractive targets for drug discovery. Through the use of high throughput screening and solution-phase parallel synthesis, inhibitors of both NF-κB and AP-1 were identified. In subsequent testing, these compounds were also shown to block both IL-2 and IL-8 levels in the same cells. One of the most potent compounds in this series, **28**, was active in several animal models of inflammation and immunosuppression, thus validating the importance of AP-1 and NF-κB as potential therapeutic targets. The synthesis and preliminary structure–activity relationships of these compounds is addressed.

## Introduction

In certain autoimmune diseases and chronic inflammatory states, the continuous activation of T-cells leads to a self-perpetuating destruction of normal tissues or organs.[1] This activation initiates a cascade of events that results in the overproduction of certain transcription factors and proinflammatory cytokines.[2,3] Transcription factors are a family of proteins that act as molecular switches and regulate several cellular events, including gene expression, cytokine production, and the synthesis of additional cellular regulators.[4]

Two transcription factors in particular, nuclear factor-κ binding (NF-κB) and activator protein-1 (AP-1), control the production of many cytokines and related proteins elevated in immunoinflammatory diseases.[5-7] These include interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNFα). NF-κB plays a significant role in the regulation of IL-8 transcription during exposure of cells to external stimuli, while AP-1 regulates both IL-2 and TNF-α production during T-cell activation. Therefore, modulation of either one or both of these transcription factors should lead to suppression of cytokine levels and, thus, represent attractive targets for the prevention of immunoinflammatory diseases.[8]

To date, no known antiinflammatory or autoimmune drugs have been specifically developed clinically as inhibitors of NF-κB and/or AP-1. Herein, we report the identification of a series of novel inhibitors of both NF-κB and AP-1 transcriptional activation and the subsequent validation of these transcription factors as drug discovery targets. Using automated high-throughput assays with stably transfected human Jurkat T-cells, we identified a compound that inhibited both NF-κB and AP-1 transcriptional activation (**1**, $IC_{50}$ = 0.3–0.5 μM).[9,10] In addition, compound **1** had a similar inhibitory effect on the production of IL-2 and IL-8 levels in stimulated cells and was active in an animal model of inflammation.[11] Through the use of solution-phase parallel chemistry and targeted synthesis, a 10-fold more potent derivative, **28**, was identified. This paper describes the use of these techniques and the resulting structure–activity relationships of this series of compounds.




**1**

## Chemistry

The compounds listed in Table 1 were prepared as illustrated in Schemes 1 and 2. The 2-amino derivatives (**2–8**) were synthesized by stirring **1** with an appropriate amine in THF. The 2-hydroxy and the 2-methoxy derivatives (**9** and **10**) were prepared by treatment of **1** with sodium hydroxide or sodium methoxide, respectively. Reduction of **1** with Pd/C/MgO in EtOH/$H_2O$ (2/1) provided **11**. The *N*-methylamide **12** was prepared by alkylation of the sodium salt of **1** with MeI. Alkylation of **1** with benzyl bromide was unsuccessful; thus, the corresponding *N*-benzyl derivative **13** was prepared using the corresponding *N*-benzylaniline.[12]

The preparation of 160 amides of general structure **15** was done using solution-phase combinatorial techniques.[13] A series of 160 commercially available alkyl-

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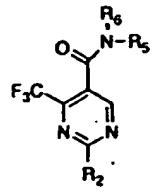
Table 1. In Vitro Evaluation of Substituted Pyrimidines



| no. | $R_2$ | $R_5$ | $R_6$ | mp (°C) | yield (%) | $IC_{50}$ (μM) NF-κB | AP-1 |
|---|---|---|---|---|---|---|---|
| 1 | Cl | H | A | 183–184 | 92 | 0.50 | 0.50 |
| 2 | $N(CH_3)_2$ | H | A | 163–164 | 80 | >10 | >10 |
| 3 | $NH_2$ | H | A | >250 | 60 | >10 | >10 |
| 4 | nBuNH | H | A | 162–163 | 41 | >10 | >10 |
| 5 | aniline | H | A | 228–229 | 91 | >10 | >10 |
| 6 | benzylamine | H | A | 202–203 | 87 | >10 | >10 |
| 7 | cyclohexylamine | H | A | 198–199 | 86 | >10 | >10 |
| 8 | piperidyl | H | A | 186–187 | 58 | 5.0 | 4.0 |
| 9 | OH | H | A | dec 160 | 68 | >10 | >10 |
| 10 | $OCH_3$ | H | A | 172–173 | 87 | >10 | >10 |
| 11 | H | H | A | 188–189 | 53 | >10 | >10 |
| 12 | Cl | $CH_3$ | A | 124–125 | 20 | 2.30 | 3.0 |
| 13 | Cl | Benzyl | A | 102–104 | 25 | 2.70 | 2.70 |
| 19 | Cl | H | B | 96–97 | 61 | >10 | >10 |
| 20 | Cl | H | C | 180–181 | 62 | >10 | >10 |
| 21 | Cl | H | D | 248–249 | 27 | >10 | >10 |
| 22 | Cl | H | E | 172–173 | 85 | 0.38 | 0.49 |
| 23 | Cl | H | F | 135–136 | 55 | 1.20 | 1.60 |
| 24 | Cl | H | G | 190–191 | 35 | 0.80 | 0.50 |
| 25 | Cl | H | H | 141–143 | 35 | 2.30 | 2.80 |
| 26 | Cl | H | I | 170–171 | 75 | 4.0 | 3.80 |
| 27 | Cl | H | J | 200–201 | 40 | 0.9 | 0.9 |
| 28 | Cl | H | K | 165–166 | 75 | 0.05 | 0.05 |

[a] Key: A = 3,5-dichlorophenyl; B = butyl; C = phenyl; D = 2,6-dimethylphenyl; E = 4-(trifluoromethyl)phenyl; F = 3,5-dimethoxyphenyl; G = 2,6-dichloro-4-pyrimidine; H = 5-methyl-2-thiophene; I = 3-methyl-5-isoxazole; J = 3,4,5-trichlorophenyl; K = 3,5-bis(trifluoromethyl)phenyl.

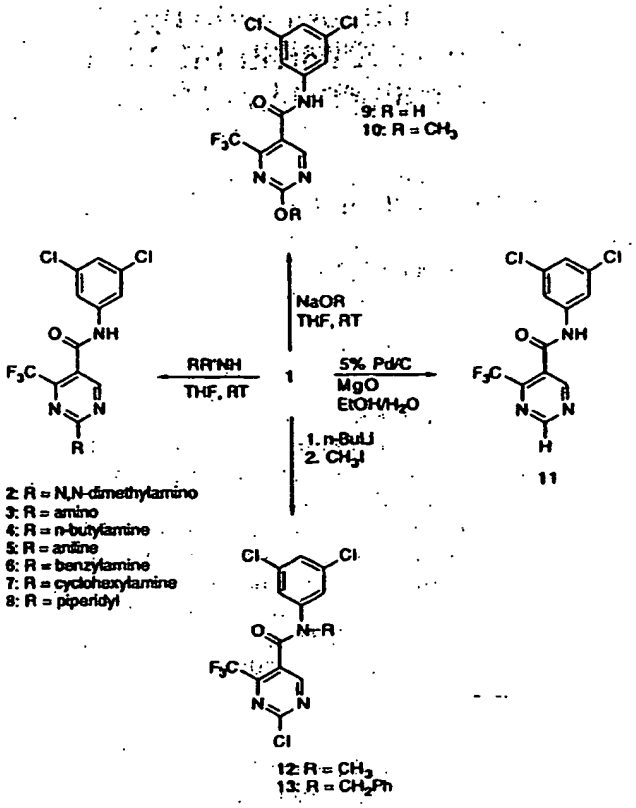
amines, anilines, and heterocyclic amines was selected for inclusion (see the Supporting Information) in this study. The compounds were prepared in a microtiter format 80 compounds at a time. The procedure involved sonicating EtOAc solutions of the amines and a slight excess of the pyrimidine acid chloride **14** in the presence of Amberlyst A-21 ion-exchange resin in a 96-well plate. A small amount of $H_2O$ was added to each well to "quench" the excess acid chloride. The organic layer from each well was transferred to individually tared test tubes (Zymark BenchMate) and concentrated. The samples were then solvated (DMSO) for high throughput screening at a concentration of 5 mg/mL. TLC analysis was done on the entire plate, and HPLC analysis was performed on 15 random samples. All samples were run in a three-point dose response analysis in the cell-based transcription assays. Yields (based upon tared weight) ranged from 60 to 90%, and purities were greater than 85%.

The 3-(trifluoromethyl)-5-carbonylanilines were prepared starting with the commercially available 3-nitro-5-(trifluoromethyl)benzoic acid (**16**) as shown in Scheme 3. Treatment of **16** with oxalyl chloride followed by the appropriate alcohol or amine provided the desired ester or amide. Reduction with Pd/C and reaction with **14** provided the compounds listed in Table 2.

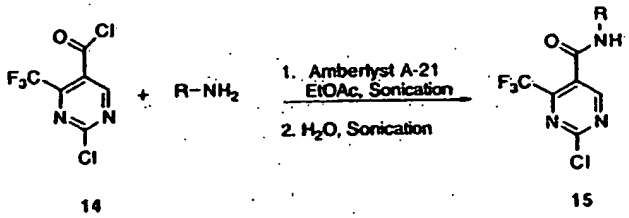
## Biology

High throughput screening and follow-up studies were performed using three distinct cell lines. Jurkat

Scheme 1




Scheme 2



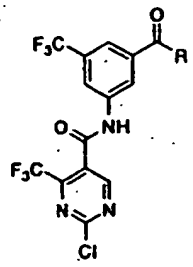

T-cells stably transfected with either an NF-κB binding site, an AP-1 binding site, or the β-actin promoter driving luciferase were pretreated for 0.5 h with compounds dissolved in 0.2% DMSO/$H_2O$. The cells were then stimulated with phorbol 12-myristate-13-acetate (PMA) and phytohemagglutin (PHA) and incubated for an additional 5 h. The cells were harvested by centrifugation for determination of luciferase activity. The results are expressed as $IC_{50}$ values where the $IC_{50}$ value is defined as the concentration of compound required to reduce luciferase activity to 50% of control values.

Cytokine determinations (IL-2 and IL-8) were performed by ELISA using commercially available kits.[14] The production IL-2 and IL-8 was determined in supernatants collected in the above luciferase studies. The results are plotted as percent of control (DMSO treated cells).

## Results and Discussion

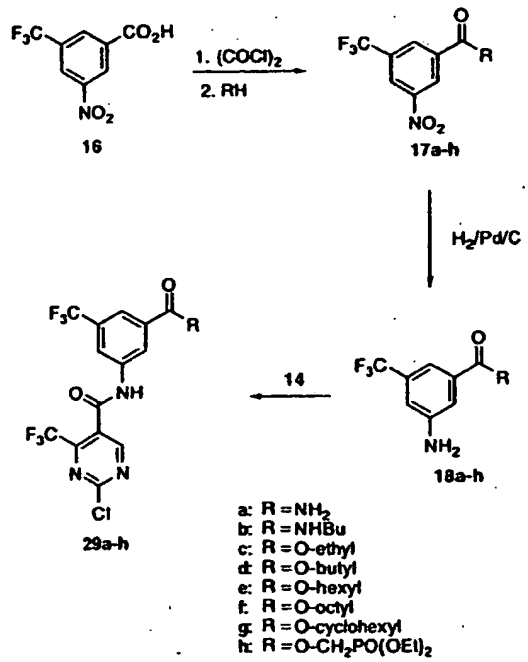
The compounds synthesized in library format were evaluated in a three-point dose response analysis (3.3, 0.3, and 0.03 μg/mL) in all three assays, and active derivatives (>50% at the 0.3 μg/mL dose) were then run

**Table 2.** In Vitro Evaluation of Substituted Pyrimidine Ester and Amides



| no. | R | mp (°C) | yield (%) | $IC_{50}$ (μM) NF-κB | $IC_{50}$ (μM) AP-1 |
|---|---|---|---|---|---|
| **29a** | $NH_2$ | 218–219 | 55 | 5.00 | 3.00 |
| **29b** | NHBu | 243–244 | 21 | >10 | >10 |
| **29c** | $OC_2H_5$ | 67–71 | 68 | 0.28 | 0.15 |
| **29d** | $OC_4H_9$ | 49–53 | 71 | 0.17 | 0.12 |
| **29e** | $OC_6H_{13}$ | 103–105 | 72 | 0.62 | 0.66 |
| **29f** | $OC_8H_{17}$ | oil | 35 | 1.80 | 1.20 |
| **29g** | *O*-cyclohexyl | 59–60 | 58 | 1.80 | 1.20 |
| **29h** | $OCH_2PO(OEt)_2$ | 125–126 | 55 | 4.60 | 3.00 |

**Scheme 3**




in a six-point dose–response analysis. Compounds in Table 1 were run immediately in a six-point dose–response analysis. None of the compounds discussed had activity on the β-actin control at the highest dose tested (3.3 mg/mL, data not shown).

The results shown in Table 1 clearly indicate the importance of the chlorine atom at the 2-position of the pyrimidine ring. Any substitution at this position besides chlorine resulted in a complete loss of activity.[15] Derivatizations of the amide nitrogen as the *N*-methyl (**12**) or *N*-benzyl (**13**) analogues resulted in a 10-fold loss of activity, and these compounds were more active against the β-actin control.

The power of the combinatorial techniques described was demonstrated by the synthesis and evaluation of 160 analogues of **1** in a 2-week period. These results allowed for an immediate assessment of the key functional groups needed at the $R_5$ position. Dramatic changes in activity were seen with the different substituents attached to the amide nitrogen. To validate this approach to lead optimization, we also synthesized individually several key derivatives in the series and compared their activity to the analogues prepared in the library.[16] Clearly, a substituted aromatic group is essential since the *n*-butyl derivative **19** and the heterocyclic amides are less active (**24**–**26**).

The most active compounds were substituted aniline derivatives. A substituent on the ring is needed at either the 3-, 4-, or 5-position. The simple aniline derivative **20** was inactive. Compound **20** was synthesized as part of the library and then prepared individually to verify the unexpected lack of activity. Several other structure–activity relationships were observed. First, aniline derivatives substituted at the 3- or 4-position with small electron-withdrawing groups were the most potent ($CF_3$ > Cl > F > $CH_3$). Large bulky groups tended to decrease activity, and substituents at the 2- and/or 6-position resulted in a loss of activity (inactive at highest concentration tested). Increasing the distance between the amide nitrogen and the aromatic rings (benzyl derivatives) also resulted in inactive compounds. The results indicated that a small electron-withdrawing group was required at either the 3- or 4-position with the best activity found with substituents at both the 3- and 5-positions or the 3- and 4-positions. Trisubstituted compounds such as the 3′,4′,5′-trichloro derivative **27** offered no advantage over the 3,5-substituted compound (**27**, $IC_{50}$ = 0.9 vs **1**, $IC_{50}$ = 0.3 μM).

On the basis of the results obtained from the solution-phase libraries, we synthesized the 3,5-bis(trifluoromethyl)aniline derivative **28** (SP100030). This compound was the most potent inhibitor identified with an $IC_{50}$ value of 50–100 nM in the cell-based assays (NF-κB and AP-1). Additional 3-(trifluoromethyl)-5-carbonyl derivatives were prepared in an effort to improve the solubility of these compounds and to further define the structure–activity relationships at the 5-position (Table 2). In summary, the ester derivatives were more active than the corresponding amides (**29b** vs **29d**), and the activity of the esters was optimal with a four carbon chain **29d**. However, all of the derivatives were less active than **28**.

The ability of compound **28** to block the production of IL-2 and IL-8 in Jurkat T-cells was also examined. As expected, both IL-2 and IL-8 were inhibited at the same concentrations as seen in the luciferase assay ($IC_{50}$ ≈ 0.03 μM). In addition, the inhibitory activity seen with this compound was specific to T-cells. Subsequent studies were conducted examining the ability of **28** to block induced cytokine production in monocytes, epithelial cells, fibroblasts, osteoblasts, or endothelial cells. Surprisingly, this compound had no activity in the other cell lines examined, although studies indicated that the compound was able to cross the cell membranes.[17] In vivo studies were conducted with **28** and the compound was active i.p. in a dose-dependent manner in several animal models of inflammation and immunosuppression.[10]

## Conclusions

Compound 28 (SP100030) represents one of the first inhibitors of NF-κB and AP-1 transcriptional activation specifically identified from high-throughput screening and solution-phase parallel synthesis. The exact mechanism of action of 28 is under investigation and will be reported shortly.[18] However, the compound has demonstrated activity in several animal models,[10] but its low aqueous solubility and high lipophilicity likely account for the lack of oral activity in the animal models tested. The activity of this series of compounds suggests that inhibitors of AP-1 and NF-κB may be useful as novel immunoinflammatory agents. Additional studies focused on further defining the structure–activity relationships of the pyrimidine ring as well as increasing the solubility of this novel class of compounds are in progress.

## Experimental Section

Starting materials were obtained from commercial sources and used without purification. Silica gel (E. Merck, 60–230 mesh) was used for flash column chromatography, and silica gel plates (E. Merck) were used for thin-layer chromatography. All NMR spectra were recorded on a Varian Gemini 300 or a Bruker AM-500 spectrometer, and shifts are reported in parts per million relative to internal tetramethylsilane. Melting points were determined on a Mel Temp II and are uncorrected. IR spectra were recorded with a Nicolet Impact 400d spectrophotometer; mass spectra were obtained on a Hewlett-Packard 5890 Series II gas chromatogram with a Hewlett-Packard 5972 mass selective detector. Combustion elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ, and found values were within 0.4% of the theoretical values (unless otherwise indicated).

**General Synthesis for the 2-Amino Derivatives (3–7). 2-(*N*,*N*-Dimethylamino)-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (2).** To a solution of 1 (100 mg, 0.270 mmol) in THF was added gaseous *N*,*N*-dimethylamine. The mixture was stirred at room temperature under an atmosphere of $N_2$ for 3 h. The reaction was concentrated, and the resulting oil was purified by column chromatography ($SiO_2$, 12/1 hexanes/EtOAc), providing 82 mg (80%) of 2 as a white solid: mp 163–164 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.89 (bs, 1H), 8.82 (s, 1H), 7.80 (s, 2H), 7.24 (s, 1H), 3.27 (s, 6H); IR (KBr) 3383, 1652, 1585 cm$^{-1}$. Anal. ($C_{14}H_{11}Cl_2F_3N_4O$): C, H, N.

**2-Amino-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)-pyrimidinecarboxamide (3):** 58% yield; mp >250 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.74 (s, 1H), 7.75 (s, 2H), 7.72 (s, 2H), 7.60 (s, 1H); IR (KBr) 3378, 1661, 1590, 1419 cm$^{-1}$. Anal. ($C_{12}H_7Cl_2F_3N_4O$): C, H, N.

**2-(*N*-Butylamino)-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (4):** 41% yield; mp 162–163 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.87 (bs, 1H), 8.81 (s, 1H), 8.71 (s, 1H), 7.80 (s, 2H), 7.24 (s, 1H), 3.50 (m, 2H), 1.62 (m, 2H), 1.41 (m, 2H), 0.93 (m, 3H); IR (KBr) 3281, 1583, 1529, 1199 cm$^{-1}$. Anal. ($C_{16}H_{15}Cl_2F_3N_4O{\cdot}0.5H_2O$): C, H, N.

**2-(*N*-Phenylamino)-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (5):** 91% yield; mp 228–229 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 8.99 (s, 1H), 7.86 (s, 2H), 7.82 (s, 2H), 7.39 (m, 2H), 7.26 (s, 1H), 7.12 (m, 1H) 2.10 (bs, 2H); IR (KBr) 3237, 1579, 1517, 1145 cm$^{-1}$. Anal. ($C_{13}H_{11}Cl_2F_3N_4O$): C, H, N.

**2-(*N*-Benzylamino)-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (6):** 87% yield; mp 202–203 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.85 (bs, 1H), 8.90 (s, 1H), 7.95 (m, 1H), 7.79 (s, 2H), 7.40 (m, 2H), 7.32 (m, 2H) 7.24 (m, 2H), 4.73 (m, 2H); IR (KBr) 3272, 1582, 1145 cm$^{-1}$.

**2-(*N*-Cyclohexylamino)-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (7):** 86% yield; mp 198–199 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.82 (bs, 1H), 8.75 (s, 1H), 7.80 (s, 2H), 7.24 (s, 1H), 3.91 (bs, 1H), 2.81 (m, 2H), 1.80 (m, 2H), 1.65 (m, 6H); IR (KBr) 1583, 1523, 1306 cm$^{-1}$. Anal. ($C_{18}H_{16}Cl_2F_3N_4O$): C, H, N.

**2-*N*-Piperidyl-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (8):** 58% yield; mp 186–187 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.85 (bs, 1H), 8.80 (s, 1H), 7.80 (s, 2H), 7.24 (d, *J* = 1.5 Hz, 1H), 3.90 (s, 4H), 1.74 (m, 2H), 1.60 (m, 4H); IR (KBr) 3267, 1583, 1531, 1267 cm$^{-1}$. Anal. ($C_{17}H_{15}F_3Cl_2N_4O$): C, H, N.

**2-Hydroxy-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (9).** A mixture of 1 (370 mg, 1.0 mmol) in THF (10 mL) and aqueous NaOH (1 M, 10 mL, 10 mmol) was stirred for 16 h at room temperature. The mixture was acidified with HCl (1 N) and extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine, and dried over $Na_2SO_4$. The solvent was removed, and the resulting crude material was purified by column chromatography ($SiO_2$, 2/1 hexanes/EtOAc) to provide 240 mg (68%) of 9 as a white solid: mp dec >160 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 8.55 (s, 1H), 8.18 (bs, 1H), 7.77 (s, 1H), 7.67 (s, 2H), 2.82 (s, 1H); IR (KBr) 3390, 1611, 1508 1216 cm$^{-1}$. Anal. ($C_{12}H_6Cl_2F_3N_3O_2$): C, H, N.

**2-Methoxy-4-(trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (10).** A mixture of 1 (100 mg, 0.27 mmol) in MeOH (15 mL) and NaOMe (50 mg, 0.92 mmol) was stirred for 2.5 h under an atmosphere of $N_2$. The reaction was acidified with HCl (1 N) and extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine, and dried over $Na_2SO_4$. The organic layer was concentrated, and the resulting crude material was purified by column chromatography ($SiO_2$, 10/1 hexanes/EtOAc) to provide 84 mg (87%) of 10 as a white solid: mp 172–173 °C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 10.1 (bs, 1H), 9.17 (s, 1H), 7.79 (s, 2H), 7.29 (s, 1H), 4.10 (s, 3H); IR (KBr) 3242, 1655, 1494, 1391 cm$^{-1}$. Anal. ($C_{13}H_8Cl_2F_3N_3O_2$): C, H, N.

**4-(Trifluoromethyl)-5-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (11).** To a solution of 1 (100 mg, 0.270 mmol) in EtOH/$H_2O$ (2/1, 2.5 mL) were added Pd/C (5%, 10 mg) and MgO (24 mg, 0.59 mmol). The mixture was stirred under an atmosphere of $H_2$ for 2.5 h, filtered through Celite, and concentrated. The resulting crude material was purified by column chromatography ($SiO_2$, 10/1 hexanes/EtOAc), providing 48 mg (53%) of 11 as a white solid: mp 189–190 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.2 (s, 1H), 9.60 (s, 1H), 9.40 (s, 1H), 7.70 (s, 2H), 7.40 (s, 1H); IR (KBr) 3262, 1650, 1585, 1151 cm$^{-1}$. Anal. ($C_{12}H_6Cl_2F_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-methyl-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (12).** To a mixture of NaH (21 mg, 0.525 mmol) in DMF (20 mL) under $N_2$ was added a solution of 1 (86 mg, 0.23 mmol) in DMF (5 mL). This was stirred for 0.3 h, MeI (0.10 mL, 1.61 mmol) was added, and stirring continued for an additional for 2 h. The solution was acidified with 1 N HCl and concentrated. The resulting oil was dissolved in EtOAc, extracted with HCl (1 N, 2 × 20 mL), and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography ($SiO_2$, 8/2 hexanes/EtOAc) to provide a solid that was recrystallized from EtOH/$H_2O$ to provide 20 mg (22%) of 12 as a white solid: mp 124–125 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.30 (s, 1H), 6.97 (s, 2H), 3.46 (s, 3H); IR (KBr) 1669, 1577, 1337 1171 cm$^{-1}$. Anal. ($C_{13}H_7Cl_2F_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-benzyl-*N*-(3′,5′-dichlorophenyl)pyrimidinecarboxamide (13).** A mixture of benzaldehyde (1.04 g, 9.40 mmol), 3,5-dichloroaniline (1.71 g, 10.6 mmol), acetic acid (0.20 mL), and methanol (100 mL was cooled to 0 °C. A solution of $NaBH_3CN$ (1 M, 28.0 mL, 28.0 mmol) was added via a syringe pump over 0.3 h. The solution was stirred at 0 °C for 0.5 h and allowed to warm to room temperature and stirring continued for 18 h. The mixture

resulting oil was partitioned between EtOAc and $H_2O$ and basified with NaOH (1 N) until pH 9. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography ($SiO_2$, 9/1 hexanes/EtOAc) to provide 1.61 g (64%) of *N*-(3,5-dichlorophenyl)benzylamine:[9] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.31 (m, 5H), 6.66 (t, $J$ = 1.8 Hz, 1H), 6.45 (d, $J$ = 1.8 Hz, 2H), 4.24 (s, 1H), 4.13 (s, 1H).

To a mixture of Amberlyst A-21 resin (1 g) and *N*-(3,5-dichlorophenyl)benzylamine (0.204 g, 0.761 mmol) in EtOAc (15 mL) was added a solution of 2-chloro-4-(trifluoromethyl)-5-pyrimidine acid chloride (0.241 g, 0.984 mmol) in EtOAc (2.0 mL). The mixture was stirred for 1 h, $H_2O$ (0.2 mL) was added, and stirring was continued for an additional 0.25 h. The organic layer was decanted and concentrated. The resulting oil was purified by column chromatography ($SiO_2$, 9/1 hexanes/EtOAc) to provide 52 mg (15%) of **13** as a clear oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.54 (s, 1H), 7.35 (m, 4H), 7.23 (m, 2H), 6.77 (m, 2H), 5.06 (s, 2H); IR (KBr) 3064, 1667, 1562 cm$^{-1}$. Anal. ($C_{19}H_{11}Cl_3F_3N_3O$): C, H, N.

**General Procedure for the Synthesis of Compounds 17a–h. 3-Nitro-5-(trifluoromethyl)benzylamide (17a).** To a solution of **16** (1.0 g, 4.2 mmol) in $CH_2Cl_2$ (50 mL) were added oxalyl chloride (1.45 mL, 18.8 mmol) and DMF (2 drops). The solution was stirred for 18 h under an atmosphere of $N_2$ and concentrated, and the resulting oil was dissolved in THF (20 mL). The solution was added to $NH_4OH$ (2.2 mL) in THF (40 mL) and stirred for 18 h. The reaction was concentrated, and the residue was partitioned between EtOAc and $H_2O$. The organic layer was washed with $H_2O$ (2×), extracted with $NaHCO_3$ (2 × 40 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude solid was purified by column chromatography ($SiO_2$, 1/1 hexanes/EtOAc) to provide 0.912 g (92% yield) of **17a** as a white solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.81 (s, 1H), 8.63 (s, 1H), 8.42 (s, 1H) 6.20 (bs, 2H); GC–MS 10.33 min (*m/e* 234, 100).

***N*-Butyl-3-nitro-5-(trifluoromethyl)benzylamide (17b):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.71 (s, 1H), 8.62 (s, 1H), 8.42 (s, 1H), 6.34 (bs, 1H), 3.52 (m, 2H), 1.66 (m, 2H), 1.45 (m, 2H), 0.98 (t, $J$ = 6.6 Hz, 3H); GC–MS 10.86 min (*m/e* 290, 99).

**Ethyl 3-nitro-5-(trifluoromethyl)benzoate (17c):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.04 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 4.51 (q, $J$ = 7.2 Hz, 2H), 1.46 (t, $J$ = 6.9 Hz, 3H); GC–MS 8.41 min (*m/e* 263, 100).

**Butyl 3-nitro-5-(trifluoromethyl)benzoate (17d):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.03 (s, 1H), 8.67 (s, 1H), 8.61 (s, 1H), 4.44 (t, $J$ = 6.6 Hz, 2H), 1.82 (m, 2H), 1.50 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); GC–MS 9.08 min (*m/e* 292, 100).

**Hexyl 3-nitro-5-(trifluoromethyl)benzoate (17e):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.04 (s, 1H), 8.68 (s, 1H), 8.62 (s, 1H), 4.43 (t, $J$ = 6.9 Hz, 2H), 1.82 (m, 2H), 1.46 (m, 6H), 0.94 (t, $J$ = 7.2 Hz, 3H); GC–MS 10.17 min (*m/e* 320, 98).

**Octyl 3-nitro-5-(trifluoromethyl)benzoate (17f):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.04 (s, 1H), 8.68 (s, 1H), 8.62 (s, 1H), 4.43 (t, $J$ = 6.9 Hz, 2H), 1.86 (m, 2H), 1.6–1.2 (m, 10H), 0.87 (m, 3H); GC–MS 11.24 min (*m/e* 348, 98).

**Cyclohexyl 3-nitro-5-(trifluoromethyl)benzoate (17g):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.03 (s, 1H), 8.67 (m, 1H), 8.61 (m, 1H), 5.10 (m, 1H), 2.0–1.3 (m, 10 H); GC 10.50 min (98).

**Diethyl phosphate methyl-3-nitro-5-(trifluoromethyl)benzoate (17h):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.06 (s, 1H), 8.71 (s, 1H), 8.63 (s, 1H), 4.74 (d, $J$ = 8.7 Hz, 2H), 4.26 (m, 4H), 1.38 (t, $J$ = 6.9 Hz, 6H).

**General Procedure for the Synthesis of Compounds 18a–h. 3-Amino-5-(trifluoromethyl)benzylamide (18a).** To a solution of **17a** (0.550 g, 2.35 mmol) in EtOH (25 mL) was added 5% Pd/C (30 mg). The mixture was flushed with $H_2$ four times and then stirred under an atmosphere of $H_2$ for 18 h. The mixture was filtered through Celite and concentrated. The resulting crude material **18a** (0.425 g, 89% yield) was used without further purification: $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 7.51(bs, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 7.10 (s, 1H), 6.70 (bs, 1H), 5.30 (bs, 2H); GC–MS 10.53 min (*m/e* 204, 98).

***N*-Butyl-3-amino-5-(trifluoromethyl)benzylamide (18b):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (s, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 6.10 (bs, 1H), 4.02 (bs, 2H), 3.46 (m, 2H), 1.61 (m, 2H), 1.43 (m, 2H), 0.96 (t, $J$ = 7.2 Hz, 3H). GC–MS 11.42 min (*m/e* 260, 99).

**Ethyl 3-amino-5-(trifluoromethyl)benzoate (18c):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (s, 1H), 7.49 (s, 1H), 7.05 (s, 1H), 4.39 (q, $J$ = 7.2 Hz, 2H), 1.40 (t, $J$ = 7.5 Hz, 3H); GC–MS 8.66 min (*m/e* 233, 96).

**Butyl 3-amino-5-(trifluoromethyl)benzoate (18d):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 7.48 (s, 1H), 7.05 (s, 1H), 4.32 (t, $J$ = 6.6 Hz, 2H), 1.75 (m, 2H), 1.48 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); GC–MS 9.79 min (*m/e* 261, 100).

**Hexyl 3-amino-5-(trifluoromethyl)benzoate (18e):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 7.49 (s, 1H), 7.05 (s, 1H), 4.31 (t, $J$ = 6.9 Hz, 2H), 2.0–1.2 (m, 8H), 0.91 (t, $J$ = 6.6 Hz, 3H); GC–MS 10.97 min (*m/e* 289, 100).

**Octyl 3-amino-5-(trifluoromethyl)benzoate (18f):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 7.48 (s, 1H), 7.05 (s, 1H), 4.31 (t, $J$ = 6.6 Hz, 2H), 4.00 (bs, 2H), 1.8–1.2 (m, 12H), 0.88 (t, $J$ = 6.9 Hz, 3H); GC–MS 11.87 min (*m/e* 317, 99).

**Cyclohexyl 3-amino-5-(trifluoromethyl)benzoate (18g):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (s, 1H), 7.50 (s, 1H), 7.08 (s, 1H), 5.00 (m, 1H), 2.0–1.3 (m, 10H); GC–MS 11.23 min (*m/e* 287, 98).

**Diethyl phosphate methyl-3-amino-5-(trifluoromethyl)benzoate (18h):** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.63 (s, 1H), 7.49 (s, 1H), 7.08 (s, 1H), 4.63 (d, $J$ = 8.4 Hz, 2H), 4.23 (m, 6H), 1.36 (t, $J$ = 7.2 Hz, 6H); GC–MS 12.6 min (*m/e* 355 M$^+$).

**General Procedure for Synthesis of the Pyrimidine Amide Derivatives. 2-Chloro-4-(trifluoromethyl)-5-*N*-butylpyrimidinecarboxamide (19).** To a 20 mL round-bottom flask were added Amberlyst A-21 ion-exchange resin (0.2 g), *n*-butylamine (0.068 g, 0.932 mmol), and EtOAc (10 mL). A solution of 2-chloro-4-(trifluoromethyl)-5-pyrimidine acid chloride (0.240 g, 0.981 mmol) in EtOAc (0.5 mL) was added to the round-bottom flask and the mixture stirred for 0.3 h. Water (0.2 mL) was added and stirring continued for 5 min. The reaction was filtered, dried over $MgSO_4$, and filtered and the solvent removed under reduced pressure. The resulting crude solid was recrystallized from EtOH/$H_2O$, providing 109 mg (61%) of **19** as a white solid: mp 96–97 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.90 (s, 1H), 5.90 (bs, 1H), 3.46 (q, $J$ = 6.75 Hz, 2H), 1.58 (m, 2H), 1.42 (m, 2H), 0.97 (t, $J$ = 7.2 Hz, 3H); IR (KBr) 3268, 1645, 1501 cm$^{-1}$. Anal. ($C_{10}H_{11}ClF_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-phenylpyrimidinecarboxamide (20):** 62% yield; mp 180–181 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.04 (s, 1H), 7.56 (d, $J$ = 7.5 Hz, 2H), 7.49 (bs, 1H), 7.41 (t, $J$ = 7.5 Hz, 2H), 7.25 (t, $J$ = 7.5 Hz, 1H); IR (KBr) 3185, 1650, 1326, 1172 cm$^{-1}$. Anal. ($C_{12}H_7ClF_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-(2′,6′-dimethylphenyl)-pyrimidinecarboxamide (21):** 27% yield; mp 248–249 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.99 (s, 1H), 9.06 (s, 1H), 7.13 (s, 3H), 2.31 (s, 6H); IR (KBr) 3235, 1661, 1353, 1155 cm$^{-1}$. Anal. ($C_{14}H_{11}ClF_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[4′-(trifluoromethyl)-phenyl]pyrimidinecarboxamide (22):** 74% yield; mp 172–173 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 11.05 (s, 1H), 9.27 (s, 1H), 7.84 (d, $J$ = 8.6 Hz, 2H), 7.64 (d, $J$ = 8.6 Hz, 2H); IR (KBR) 3290, 1667, 1535, 1337 cm$^{-1}$. Anal. ($C_{13}H_6ClF_6N_3O$·0.5$H_2O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-(3′,5′-dimethoxyphenyl)pyrimidinecarboxamide (23):** 55% yield; mp 135–136 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.01 (s, 1H), 7.56 (s, 1H), 6.77 (s, 1H), 6.76 (s, 1H), 6.34 (t, $J$ = 1.5 Hz, 1H), 3.81 (s, 6H); IR (KBR) 3290, 1661, 1606, 1568 cm$^{-1}$. Anal. ($C_{14}H_{11}ClF_3N_3O_3$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[4-(2′,6′-dichloropyridino)]pyrimidinecarboxamide (24):** 40% yield; mp 189–190 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.02 (s, 1H), 8.10 (s, 1H), 7.59 (s, 2H); IR (KBr) 1711, 1579, 1210, 1167 cm$^{-1}$. Anal. ($C_{11}H_4Cl_3F_3N_4O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[2′-(5″-methylthiopheneyl)]pyrimidinecarboxamide (25):** 21% yield; mp 142–143 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.02 (s, 1H), 8.22 (s, 1H), 6.63 (m, 1H), 6.56 (m, 1H), 2.46 (s, 3H); IR (KBr) 3246, 1651, 1563, 1326 cm$^{-1}$. Anal. ($C_{11}H_7ClF_3N_3OS$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[5′-(3″-methylisoxazolyl)]pyrimidinecarboxamide (26):** 75% yield; mp 170–171 °C; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 9.42 (s, 1H), 6.74 (s, 1H), 2.27 (s, 3H); IR (KBr) 1704, 1562, 1209 cm$^{-1}$. Anal. ($C_{10}H_6ClF_3N_4O_2$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-(3′,4′,5′-trichlorophenyl)pyrimidinecarboxamide (27):** 40% yield; mp 200–201 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.48 (bs, 1H), 8.91 (s, 1H), 7.85 (s, 2H), 7.59 (s, 2H); IR (KBr) 1706, 1561, 1203 cm$^{-1}$. Anal. ($C_{12}H_4Cl_4F_3N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′,5′-bis(trifluoromethyl)phenyl]pyrimidinecarboxamide (28):** 75% yield; mp 166–167 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.05 (s, 1H), 8.10 (s, 2H), 7.86 (s, 1H), 7.76 (s, 1H); $^{13}$C NMR (300 MHz, acetone-$d_6$) $\delta$ 162.9, 141.2, 133.4, 132.9, 128.2, 126.3, 122.8, 122.7, 121.0, 118.7; IR (KBr) 3292, 1668, 1517, 1380 cm$^{-1}$. Anal. ($C_{14}H_5ClF_9N_3O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-(aminocarbonyl)phenyl]pyrimidinecarboxamide (29a):** 55% yield; mp 218–219 °C; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 10.41 (bs, 1H), 9.45 (s, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.07 (s, 1H), 7.84 (bs, 1H), 6.67 (bs, 1H); IR (KBr) 1677, 1559, 1339, 1211 cm$^{-1}$. Anal. ($C_{14}H_7ClF_6N_4O_2$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-[(*N*-butylamino)carbonyl]phenyl]pyrimidinecarboxamide (29b):** 21% yield; mp 243–244 °C; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 10.38 (bs, 1H), 9.44 (s, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 8.09 (bs, 1H), 7.99 (s, 1H), 3.42 (q, $J$ = 6.6 Hz, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 0.93 (t, $J$ = 7.2 Hz, 3H); IR (KBr) 1652, 1586, 1360, 1211 cm$^{-1}$. Anal. ($C_{18}H_{15}ClF_6N_4O_2$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-(ethoxycarbonyl)phenyl]pyrimidinecarboxamide (29c):** 30% yield; mp 69–71 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.06 (s, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.17 (s, 1H), 7.94 (bs, 1H), 4.43 (q, $J$ = 6.9 Hz, 2H), 1.43 (t, $J$ = 6.9 Hz, 3H); IR (KBr) 1694, 1575, 1355, 1262 cm$^{-1}$. Anal. ($C_{16}H_{10}ClF_6N_3O_3$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-(butoxycarbonyl)phenyl]pyrimidinecarboxamide (29d):** 71% yield; mp 49–53 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.12 (bs, 1H), 9.04 (s, 1H), 8.29 (m, 2H), 8.08 (s, 1H), 4.29 (t, $J$ = 6.6 Hz, 2H), 1.76 (m, 2H), 1.46 (m, 2H), 0.98 (t, $J$ = 7.2 Hz, 3H); IR (KBr) 1708, 1574, 1267 cm$^{-1}$. Anal. ($C_{18}H_{14}ClF_6N_3O_3 \cdot 0.5H_2O$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-[(hexyloxy)carbonyl]phenyl]pyrimidinecarboxamide (29e):** 72% yield; mp 103–105 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.07 (s, 1H), 8.31 (s, 1H), 8.15 (s, 1H), 7.86 (bs, 1H), 4.38 (t, $J$ = 7.2 Hz, 2H), 1.8–0.8 (m, 11H); IR (KBr) 1704, 1560, 1350, 1206 cm$^{-1}$. Anal. ($C_{20}H_{18}ClF_6N_3O_3$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-[(octyloxy)carbonyl]phenyl]pyrimidinecarboxamide (29f):** 35% yield; oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.05 (s, 1H), 8.73 (s, 1H), 8.30 (s, 1H), 8.21 (s, 1H), 8.07 (s, 1H), 4.22 (t, $J$ = 6.6 Hz, 2H), 1.76 (m, 2H), 1.31 (m, 10H), 0.86 (m, 3H); IR (KBr) 3306, 1689, 1562, 1359 cm$^{-1}$; HRMS calcd for $C_{22}H_{22}ClF_6N_3O_3$ 526.1332, found 526.1339 ($MH^+$).

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-[(cyclohexyloxy)carbonyl]phenyl]pyrimidinecarboxamide (29g):** 58% yield; mp 59–60 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.06 (s, 1H), 8.31 (s, 1H), 8.21 (s, 1H), 8.13 (m, 2H), 5.02 (m, 1H), 2.04–1.23 (m, 10H); IR (KBr) 3295, 1689, 1568, 1348 cm$^{-1}$. Anal. ($C_{20}H_{16}ClF_6N_3O_3$): C, H, N.

**2-Chloro-4-(trifluoromethyl)-5-*N*-[3′-(trifluoromethyl)-5′-[[(dimethyl phosphate)methoxy]carbonyl]phenyl]pyrimidinecarboxamide (29h):** 55% yield; mp 125–126 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.89 (s, 1H), 9.35 (s, 1H), 8.65 (s, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 4.54 (d, $J$ = 8.1 Hz), 4.08 (m, 4H), 1.37 (t, $J$ = 7.2 Hz, 6); IR (KBr) 1739, 1573, 1365 cm$^{-1}$. Anal. ($C_{19}H_{17}ClF_6N_3O_6P$): C, H, N.

**Solution-Phase Library Preparation.** Amberlyst A-21 ion-exchange resin (5–10 beads) was placed into 80 wells of a 1 mL deep well microtiter plate (rows 1 and 12 open). The 80 individual amines as shown in Table 2 (100 $\mu$L, 22.4 $\mu$mol in EtOAc) were added to the individual wells and diluted with additional EtOAc (0.2 mL). Then to each well was added a solution of 2-chloro-4-(trifluoromethyl)-5-pyrimidine acid chloride (100 $\mu$L, 24.6 $\mu$mol) in EtOAc. The wells were capped, and the plate was sonicated in a desk top sonicator (Branson 1210) for 0.25 h. To each well was added $H_2O$ (30 $\mu$L), and the plate was sonicated for an additional 0.1 h. The organic layer (280 $\mu$L) of each well was transferred into a tared test tube and concentrated to provide 80 individual compounds. Each compound was analyzed by TLC (1/1 hexanes/EtOAc), and 15 random samples were analyzed by HPLC. The test tubes were then solvated at 5 mg/mL and submitted for biological testing.

**NF-$\kappa$B Assay.** Human Jurkat T-Cells stably transfected with an NF-$\kappa$B binding site (from the MHC promoter) fused to a minimal SV-40 promoter driving luciferase were used in these experiments.[19] Cells were counted, resuspended in fresh medium containing 10% Serum-Plus at a density of $1 \times 10^6$ cells/mL, and plated in 96-well round-bottom plates (200 $\mu$L per well) 18 h prior to running the assays.

Compounds dissolved in 0.2% DMSO/$H_2O$ at the appropriate concentrations (3.3, 0.33, and 0.03 $\mu$g/mL for initial evaluation of libraries) were then added to the microtiter plates containing the cells, and the plates were incubated at 37 °C for 0.5 h. To induce transcriptional activation, 50 ng/mL of phorbol 12-myristate-13-acetate (PMA) and 1 $\mu$g/mL of phytohemagglutin (PHA) were added to each well, and the cells were incubated for an additional 5 h at 37 °C. The plates were centrifuged at 2200 rpm for 1 min at room temperature followed by removal of the media; 60 $\mu$L of cell lysis buffer was added to each well, and cells were lysed 0.25 h; 40 $\mu$L of each cell lysate was transferred to a black 96-well plate, and 50 $\mu$L of luciferase substrate buffer was added. Luminescence was immediately measured using a Packard TopCount. The results are expressed as $IC_{50}$ values where the $IC_{50}$ value is defined as the concentration of compound required to reduce luciferase activity to 50% of control values.

**AP-1 Assay.** The AP-1 assay was run as described above for NF-$\kappa$B except that the Jurkat T-Cells were stably transfected with a plasmid that contained an AP-1 binding site from the collagenase promoter driving luciferase expression.[19] In addition, the concentrations of PMA and PHA were 5 ng/mL and 1 $\mu$g/mL, respectively.

**$\beta$-Actin Assay.** The $\beta$-actin assay was run as described above for NF-$\kappa$B except that the Jurkat T-Cells were stably transfected with a plasmid that contained the $\beta$-actin promoter driving luciferase and the cells were not induced with PMA and PHA.

**Inhibition of Cytokines.** After centrifugation, supernatants from each well in the above luciferase experiments were collected and stored at −20 °C until assay. Approximately 20–50 $\mu$L aliquots were removed and cytokine levels determined by ELISA (Biosource International, IL-2 (AP-1) and IL-8 (NF-$\kappa$B)). The results are expressed as $IC_{50}$ values where the $IC_{50}$ value is defined as the concentration of compound required to reduce cytokine levels to 50% of control values.

**Supporting Information Available:** Amine, aniline, and heterocyclic amine structures for library and HTS data for combinatorial plates (19 pages). Ordering information is given on any current masthead page.

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